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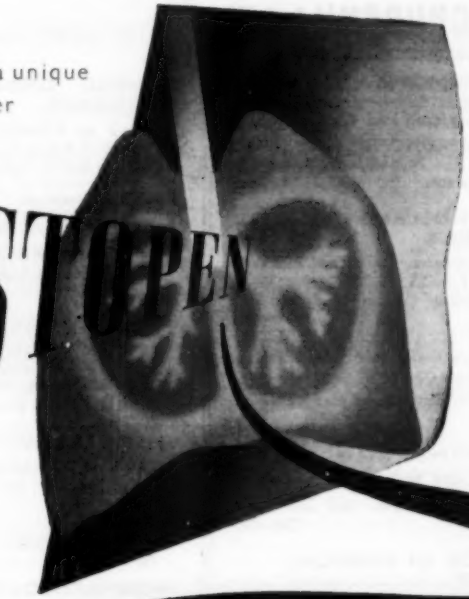

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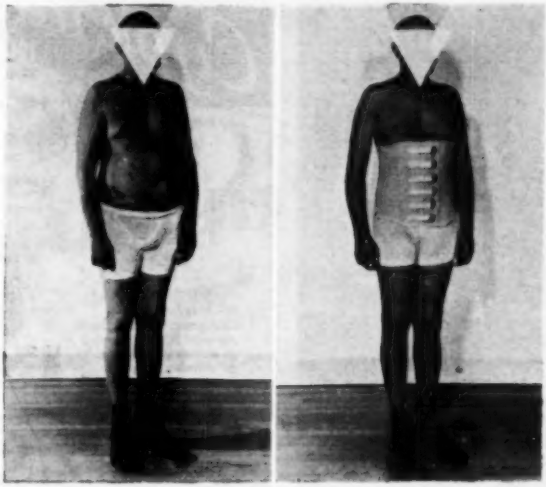

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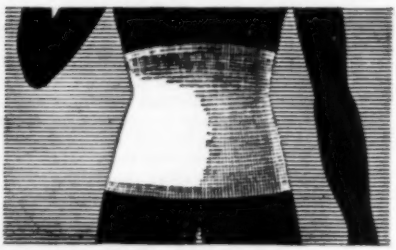

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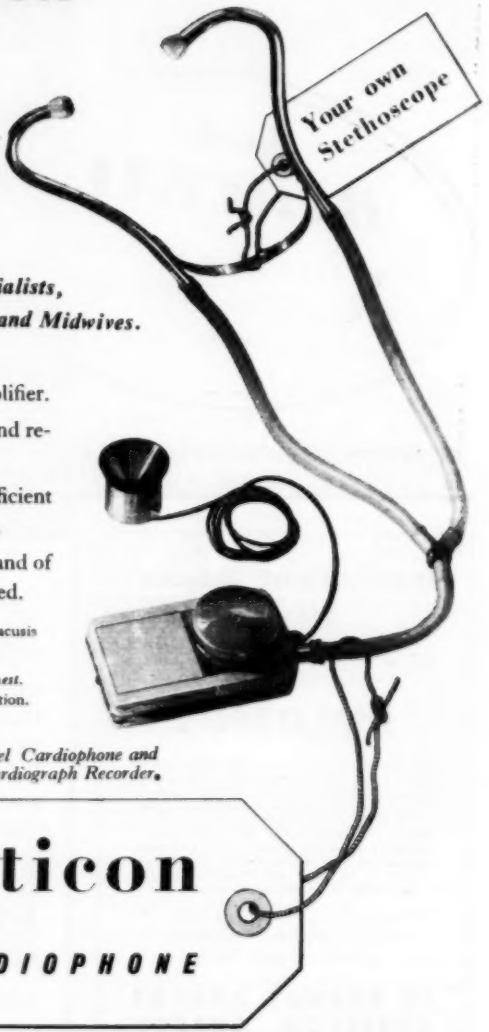

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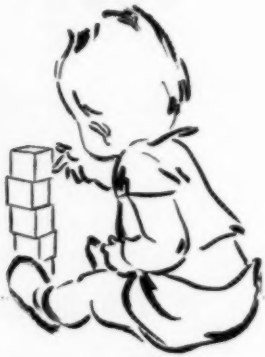

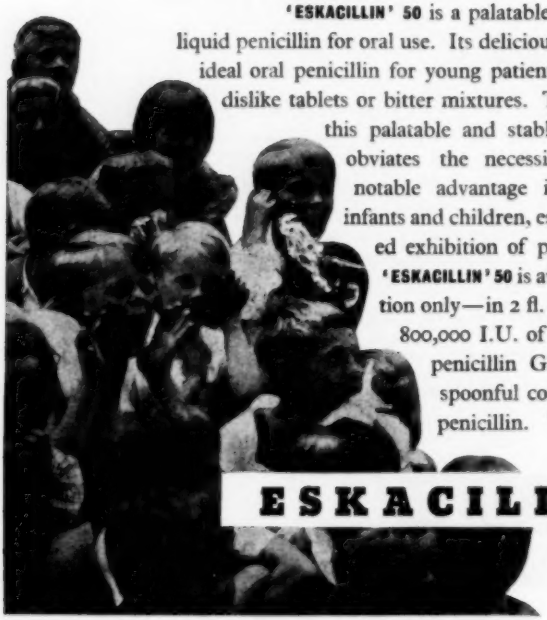

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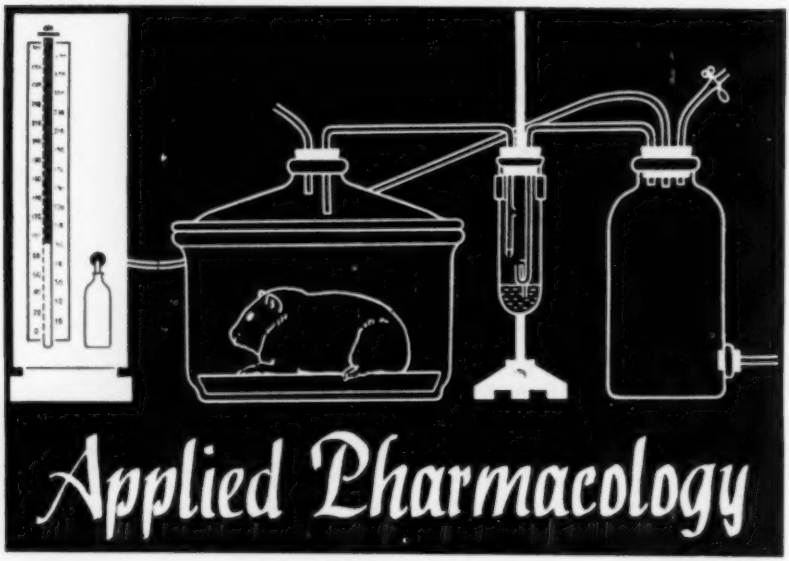

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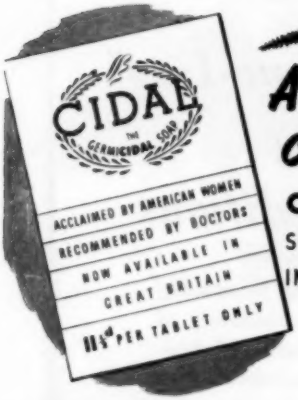

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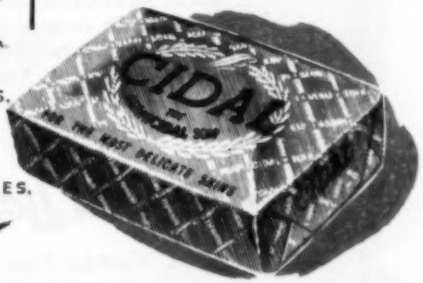
Hexachlorophene (2:2'—dihydroxy—3:5:6:3':5':6'—hexachlorodiphenylmethane) is a recently developed germicide tested extensively in America. Colourless, odourless, non-irritant and non-toxic, it has the valuable property of being retained on the skin. 125 times more efficient than carbolic acid at 37°C. against Staphylococcus aureus, it possesses a high dilution coefficient.

FOR PERSONAL USE IN

- SURGERIES, HOSPITALS,
- SCHOOLS & HOMES
- INVALUABLE WHERE PEOPLE GATHER IN FACTORIES, OFFICES, HOTELS ETC.



Guaranteed to contain 2% Hexachlorophene

MADE BY J. BIBBY & SONS LTD · LIVERPOOL 3

Reducing the "Time-Lag" in treating Rheumatic Conditions

DESPITE half a century of painstaking research, there is still no unanimity of opinion regarding the causation of rheumatic diseases. Treatment is therefore necessarily symptomatic and directed to the relief of pain.

Massage has long been the treatment of choice. But usually in severe cases, adequate massage cannot as a rule begin at once; the affected muscles are too taut and tender. Days or even weeks may have to elapse before the patient can benefit from the stimulating effects of deep massage.

This " time lag " has now been eliminated by the use of Lloyd's Adrenaline Cream.

Gently massaged into the affected area, the cream causes quick relaxation of the tense muscles and almost *immediate* relief from pain.

Reports of the successful treatment of hundreds of rheumatic patients have appeared recently in leading medical journals, recommending Lloyd's Adrenaline Cream as the most satisfactory preparation.

Supplies of Lloyd's Adrenaline Cream are now available through Boots, Timothy Whites & Taylors, and all pharmacists.

Howard Lloyd + Co. Ltd.

11 *Waterloo Place, London, S.W.*1

Makers of Fine Pharmaceuticals since 1880

the central nervous stimulant of choice

Towards the evening of life in old age; in the maturity of the climacteric years; during convalescence from severe illness — or at any other time when depression affects the well-being of the patient — 'Dexedrine' is the central nervous stimulant of choice. In depression, 'Dexedrine' dispels the characteristic symptom of chronic fatigue, restores mental alertness, and revives normal interest, activity and zest for living.

'Dexedrine'

tablets

Each tablet contains 5 mg. dextro-amphetamine sulphate

MENLEY & JAMES, LIMITED, 123 COLDHARBOUR LANE, LONDON, S.E.5

for Smith Kline & French International Co., owner of the trade mark 'Dexedrine.

DP41

THE *Kylon* TRADE MARK METHOD OF VAGINAL THERAPY

. . employs disposable applicators with medicated jellies in all vaginal conditions for which soluble pessaries are commonly used.

The following medicaments are available—

Acetarsol • Lactic Acid
Sulphathiazole • Oestrone
Proflavine • Ichthammol
Gentian Violet
Acetarsol Combination *(active against Trichomonas and associated infections).*

Prescribe "Kylon applicator set" stating type of jelly, e.g. "Kylon Acetarsol applicator set—use one application nightly (or according to requirements)."

ADVANTAGES

- Deep placement without digital insertion.
- Instant distribution of jelly over vaginal surfaces.
- Prolonged retention of jelly with consequent economy in use.

PACKS

Single sets each containing 1 tube of medicated jelly and 12 KYLON applicators *(patent pending)*. Also in HOSPITAL PACKS.

Professional sample and literature gladly sent on request to: Medical Department,
KYLON LIMITED, EAGLE HOUSE, JERMYN STREET, LONDON S.W.1.

She deserves a good breakfast

Nidoxital

CAPSULES

for effective control of the nausea and vomiting of pregnancy

provide immediate and prolonged effect by the additive action of their five ingredients . . . . benzocaine, pentobarbital sodium, nicotinamide, dl-methionine and pyridoxine hydrochloride . . . . logically combined to control those physiologic changes of early pregnancy which may initiate hyperemesis gravidarum.

Nidoxital

- *reduces alimentary peristalsis and gastric excitability.*
- *depresses sensitivity of vomiting centre.*
- *lowers reflex excitability of stomach.*
- *assists fatty acid and protein metabolism.*
- *tends to maintain hepatic function and aids the liver in detoxification.*

For Prescription . . . .
IN BOTTLES OF 20 ORAL CAPSULES

LITERATURE ON REQUEST

Ortho Pharmaceutical Limited
HIGH WYCOMBE · BUCKINGHAMSHIRE
ENGLAND

Makers of Gynaecic Pharmaceuticals

Vital Restoration

When restoration of the blood picture is vital, 'Lextron' can be relied upon to stimulate both erythrocyte and hæmoglobin formation. It has achieved considerable success in the treatment of various types of anæmia and, in particular, the anæmias of pregnancy have shown a prompt response to treatment. Whether anæmia exists or not, 'Lextron' is of value in many clinical conditions characterised by loss of appetite, weakness or under-nutrition.

'PULVULES' No. 55 'LEXTRON'

Each filled capsule contains:

Liver-Stomach Concentrate	0.455 gm.
Green Iron and Ammonium Citrate	0.2 gm.
Aneurine Hydrochloride	0.15 mg.
Riboflavin	0.05 mg.

Supplied in packages of 42, 84 and 500.

Lilly trade marks are identified by single quotation marks.

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NOW FREELY AVAILABLE

ELI LILLY AND COMPANY LIMITED, BASINGSTOKE, HANTS

In this room of the Sterile Area at our Speke premises operators are filling penicillin into vials under the most rigorous aseptic conditions

'DISTAQUAINE' G
brand

Dry substance consisting of procaine penicillin and suspending agents for the extemporaneous preparation of an aqueous suspension for intramuscular injection.

'DISTAQUAINE' *FORTIFIED*
brand

Dry substance consisting of procaine penicillin plus potassium penicillin and suspending agents for the preparation of an aqueous suspension. The inclusion of the potassium salt provides an immediately accessible dose of soluble penicillin in addition to the prolonged action of the more slowly absorbed procaine salt.

'DISTAQUAINE' *SUSPENSION*
brand

'Distaquaine' G in ready prepared aqueous suspension, an additional convenience for the busy practitioner.

Distributed by :
ALLEN & HANBURYS LTD.
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Advantages of 'DISTAQUAINE' brand preparations

- *Aqueous, containing neither oil nor wax*
- *Easy to prepare and administer*
- *Least possible pain on injection*
- *Effective blood levels up to 24 hours following administration*
- *Dry syringe unnecessary*
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THE DISTILLERS COMPANY (BIOCHEMICALS) LIMITED

SPEKE LIVERPOOL

'DISTAQUAINE,' *trade mark, is the property of the manufacturers*

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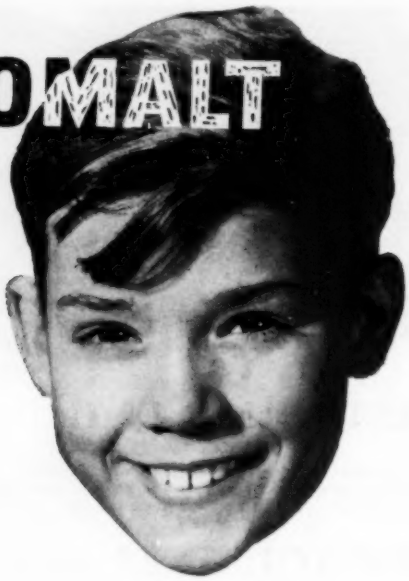

The Nutritious Children's Tonic

Ferromalt is rich in the B-Complex vitamins, protein, mineral salts and diastase. To these are added Collosol Ferro-cuprum (colloidal iron and copper), vitamin D and concentrated orange juice. Ferromalt is most suitable for children. It is readily digested and assimilated: the colloidal iron does not stain the teeth or cause constipation: the addition of vitamin D ensures absorption of calcium: finally, the flavour appeals to young palates.

THE CROOKES LABORATORIES LIMITED · PARK ROYAL · LONDON N.W.10

for burns

'CETAVLON' CETRIMIDE B.P.
TRADE MARK

'Cetavlon' is a highly effective bactericidal and cleansing agent of particular value in the treatment of burns, wounds, etc.

Pleasant to handle and economical in use, 'Cetavlon' also possesses these important advantages.

- All contaminating matter quickly and easily removed.
- Highly bactericidal in low concentration, against both Gram-positive and Gram-negative bacteria.
- Non-toxic and non-irritant.
- Does not retard healing.

From your wholesaler or, in case of difficulty, apply to your nearest I.C.I. Sales Office—London, Bristol, Birmingham, Manchester, Glasgow, Edinburgh, Belfast and Dublin.

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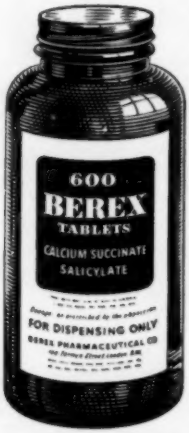

BEREX
REG. TRADE MARK

SUCCINATE – SALICYLATE THERAPY

IN THE RHEUMATIC DISORDERS

Licensed under DOLCIN Patent
Patented in Great Britain, 642971

Succinate Therapy is predicated on its role as a physiological respiratory catalyst correcting the impairment in tissue oxidation. Furthermore, succinate obviates the toxic effect of salicylate thereby enabling massive and prolonged dosage when indicated.

Each tablet contains :— **Calcium-Succinate** ..... **2.8 grs.**
Acetylsalicylic acid ..... **3.7 grs.**

Available in bottles of 100 and 600 tablets to the medical profession only

Professional sample and literature on request to :

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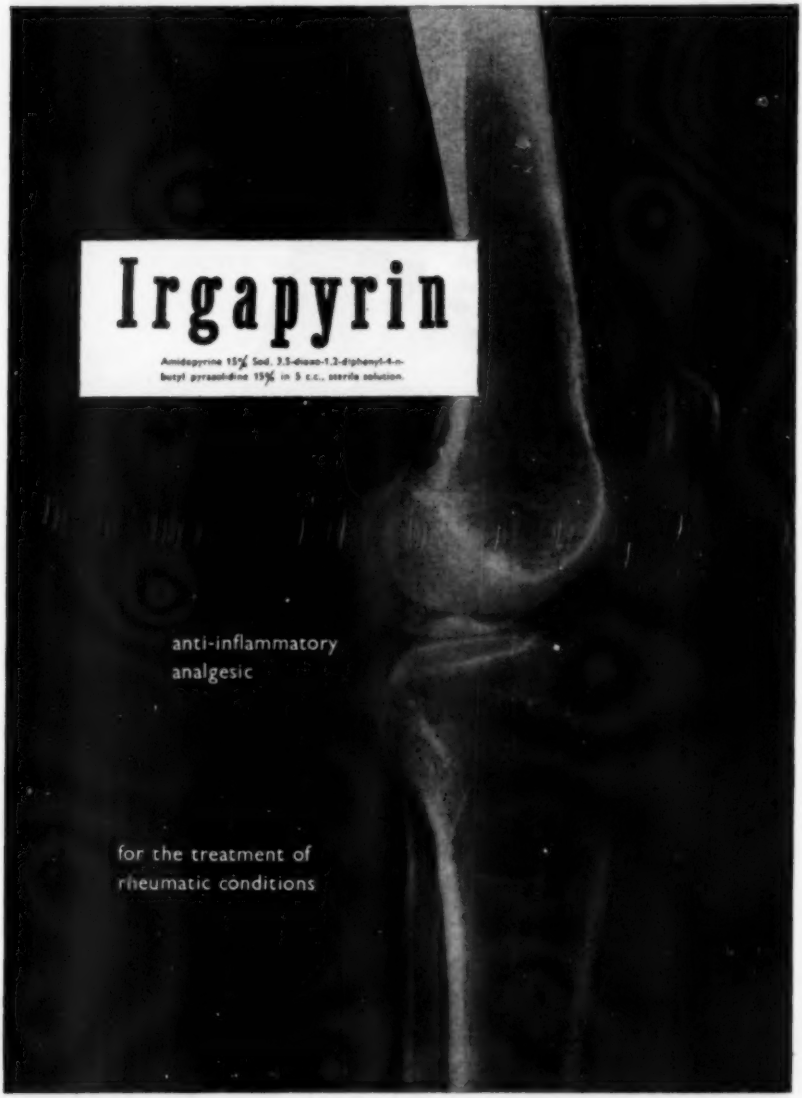
Medical Department, 109 Jermyn Street, London, S.W.1



In tubes of 5 and 50 ampoules. Literature and samples on request from:

PHARMACEUTICAL LABORATORIES GEIGY LIMITED

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In the treatment of —

ANGINA PECTORIS, BRONCHIAL ASTHMA,
CORONARY THROMBOSIS, CHRONIC COR PULMONALE

A highly purified form of KHELLIN, the active principle obtained from the seeds of the Eastern Mediterranean plant Ammi visnaga (LINN)

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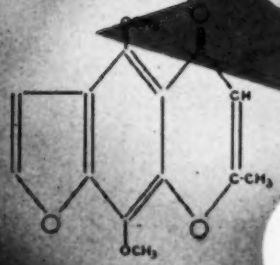

Produces a rapid yet prolonged action without lowering the blood pressure.

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COMPOUND AMINACRINE TULLE

CONFORMING TO THE SPECIFICATION FOR COMPOUND AMINACRINE TULLE OF THE DRUG TARIFF PUBLISHED BY THE MINISTRY OF HEALTH.

Special Announcement

We take great pleasure in informing the Medical Profession that on and after

1st OCTOBER 1951

the Ministry of Health will include Compound Aminacrine Tulle in the Drug Tariff and from this date Cimlac Gauze may be prescribed on Form E.C.10.

CIMLAC GAUZE

Non-greasy, non-adherent, and safe in the hands of patients.

Available on prescription as follows :—

Cartons of 10 pieces ... ... 3½" x 3½"
Each piece individually packed in heat sealed, cellulose film envelopes, with full directions for use.

Single pieces ... ... 3½" x 3½"
Packed in heat sealed, cellulose film envelopes, with full directions for use.

Please address enquiries to :—
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TELEPHONE : CREWE 3251 (5 lines)

CALMIC LIMITED · *Manufacturing Chemists* · CREWE HALL · CREWE

GELUSIL

* TRADE MARK REGD.

Antacid Adsorbent

Gelusil* combines the therapeutic advantages of a uniquely stable aluminium hydroxide with those of magnesium trisilicate and is a highly effective product for the treatment of gastric hyperacidity and peptic ulcer. A specially prepared colloidal aluminium hydroxide, virtually impervious to hydrochloric acid in physiological concentrations is employed in Gelusil. This ensures that the demulcent, colloid character of Gelusil is not altered by contact with the gastric contents; thus constipation is prevented. The combination of magnesium trisilicate with aluminium hydroxide adds prolonged action to prompt acid adsorption: this rapid and prolonged neutralization of excessive gastric acidity makes possible less frequent medication with welcome economy to the patient.

INDICATIONS. For the treatment of gastric hyperacidity and peptic ulcer. To provide prompt and prolonged antacid action with a mucilaginous protective covering over the ulcer crater. Gelusil may be taken with other medication such as phenobarbitone and belladonna.

PACKING

Cellulose film wrapped in boxes of 50. Also, for dispensing only, in bulk packages of 500 unwrapped; not subject to Purchase Tax on prescription.

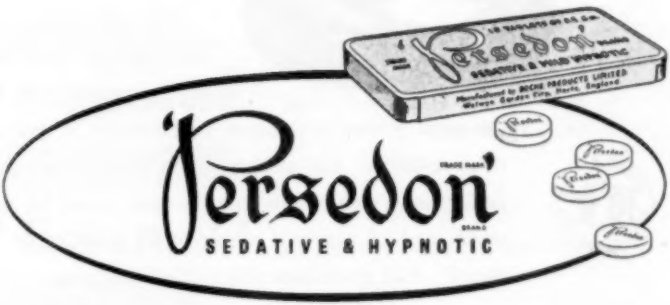
FORMULA. *Each tablet contains:—Mag. Trisil. 7½ grs. Alum. Hydrox. gel 4 grs.*

NO WARNER PREPARATION HAS EVER BEEN ADVERTISED TO THE PUBLIC

William R. WARNER and Co. Ltd. Power Road, London W.4.

Day and Night Sedation

Small doses of 'Persedon' provide excellent day-time sedation for the tense, restless and anxious type of patient. It may also be prescribed with advantage for the patient who has interrupted or restless sleep or who wakes during the night. For severe chronic insomnia 'Persedon' may be given to reinforce the action of the more powerful hypnotics.



ROCHE PRODUCTS LIMITED

Midwives carry it lightly

MINNITT MINOR

The New—Really Portable Gas/Air Analgesia Equipment

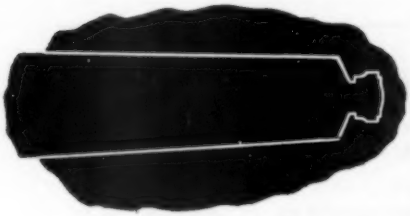
Constructed of strong, light material throughout, this new Minnitt Minor apparatus weighs less than 13 lbs, complete with filled cylinder. It is the lightest, most convenient Gas/Air equipment in the world. Designed primarily to carry a lightweight 50 gallon Nitrous oxide cylinder, this strongly built little apparatus gives a performance comparable with the existing well known Minnitt series, and of course is approved by the Central Midwives Board. Full particulars will gladly be supplied on request.

COXETER-KING MEDICAL SECTION

THE BRITISH OXYGEN CO. LTD

LONDON AND BRANCHES

Incorporating **A. CHARLES KING LIMITED**



'The clinician is well advised to attach almost as much importance to the choice of vehicle for his remedy as to the choice of the remedy itself.'

Modern Practice in Dermatology. (1950) *London: Butterworth, p.* 777.

In **'Eskamel'** —(resorcinol 2%, sulphur 8%) the vehicle is designed specifically to aid the treatment of acne; it is entirely free from grease or oil and its delicate flesh tint masks unsightly lesions.

In **'Pragmatar'** —(cetyl-alcohol-coal-tar distillate 4%, sulphur 3%, salicylic acid 3%) the vehicle assists easy application and removal of the preparation, even when used on a hairy surface.

In both 'Pragmatar' and 'Eskamel'—the vehicles enhance the therapeutic effect of their active ingredients and make these preparations cosmetically acceptable and pleasant to use.

'Pragmatar' *highly effective in a wide range of common skin disorders*

'Eskamel' *a significant advance in acne therapy*

MENLEY & JAMES, LIMITED, Coldharbour Lane, London, S.E.5
for *Smith Kline & French International Co., owner of the trade marks 'Pragmatar' and 'Eskamel'*
FREMP101

ASPIRIN is an acidic substance, sparingly soluble.

DISPRIN is neutral, stable, soluble – and palatable.

The reasons for preferring calcium aspirin to aspirin lie chiefly in the fact that it is a neutral, soluble and bland compound, whereas aspirin is acidic, sparingly soluble and may act as a gastric irritant.

But calcium aspirin has a defect of its own – chemical instability; and in consequence attempts to manufacture it in the form of tablets that could be depended upon to remain free of nauseous breakdown products, under reasonable conditions of storage, have hitherto met with little success. These difficulties have now been overcome. 'Disprin,' a stable, tablet preparation, readily dissolves to yield a substantially neutral and palatable solution of calcium aspirin that can be prescribed in all conditions in which acetylsalicylate administration is indicated.

Extended clinical trials show that Disprin in massive dosage, even over long periods, can be tolerated without the development of gastric or systemic disturbances except in cases of extreme hypersensitivity.

DISPRIN REG.

Neutral, stable, soluble, palatable calcium aspirin

On prescription Disprin is free of Purchase Tax.
Clinical sample and literature supplied on application.

RECKITT & COLMAN LTD., HULL AND LONDON. (PHARMACEUTICAL DEPT., HULL)

Introducing

PRUVAGOL

(Diamino-disulphomethyl-fuchsonium sulphonate)

for the conquest of

PRURITUS VULVÆ

Successful trials in leading British hospitals have enabled us to introduce PRUVAGOL for the swift and complete relief of Pruritus Vulvæ without the use of mercurials and local anæsthetics.

"70 patients complaining of vaginal discharge and pruritus have so far been treated, the average duration of the complaint being 2 years. The cream was applied to the cervix and vagina every second day. After the first or second application all irritation disappeared and in the average case the discharge ceased after five applications."

Ref.: **Non-Specific Cervicitis.** B.M.J., 14.7.1951

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Prescribed on E.C. 10 Forms

In tubes with applicators and special packs for hospitals and clinics.

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Sole Agent for India: Messrs CAMA NORTON & CO., 23 Medows St., Bombay

·Pabyrn·

Proteolysed Liver B.P.C

Indications : all forms of macrocytic anaemia, refractory anaemia, hypoproteinaemia, coeliac disease, sprue, anaemia of pregnancy and lactation, tuberculosis, debility, pre-operative and post-operative.

Brochure supplied on request :

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Camp LUMBOSACRAL Supports

Camp Lumbosacral Supports have extended height above the waist-line at the back and a special adjustable strap designed to hold the upper portion snugly against the lumbar region. The double side-lacing adjustments ensure the prescribed degree of regulated close support to the lumbosacral and sacro-iliac areas.

Illustrated: An example from the Camp series of basic lumbosacral supports.

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Anatomical Supports

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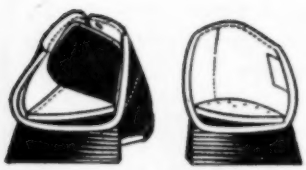
KCR508

'INNERAZE'

shoes by START-RITE



These cross-sections show the built-in wedge in position and the buttressed heel. The thickness of the wedge is ⅛" or ¼" according to size of shoe.

For names and addresses of the Start-rite dealers from whom 'Inneraze' shoes can be obtained please write to:—

'Inneraze' shoes for children are to the Orthopædic Surgeon as commercial sutures to the general surgeon.

Supplied on medical prescription only, they incorporate the necessary surgical alterations for the treatment of flat feet (pronation) . . . by means of in-built wedging. The wedge is an integral part of the shoe, and is located between the inner and outer sole. These alterations are uniform . . . avoid shoe distortion and consequent uneven wear . . . do not mar the appearance of the shoe.

The Surgeon is relieved of the necessity for checking up that the "alterations" are those that are needed, and of time-consuming supervision after each repair.

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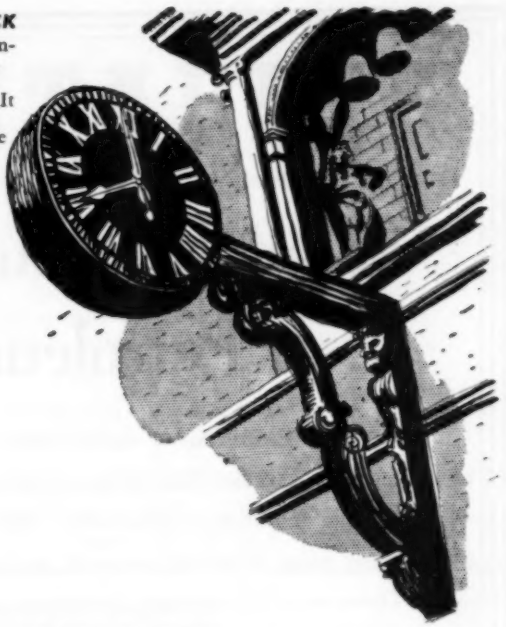
ST. DUNSTAN'S CLOCK
On the wall of St. Dunstan-in-the-West in Fleet Street is the first clock showing minutes ever to be made. It was also the first clock to have two dials. It was made in 1671.



CLOCKWORK REGULARITY. Normal bowel action is a fine thing to possess. It is, perhaps, the most sought after talisman against ill-health in the world. No wonder, then, if its temporary suspension leads from a mild despondency even to black despair. But in such a crisis panic measures are to be avoided—the taking of harsh purgatives eschewed.

Success in the restoration of the much-cherished habit lies in the regular persuasive stimulus of soft bulk—such as is provided by 'PETROLAGAR.' Gently and unobtrusively, 'PETROLAGAR' arranges for normal physiological evacuations and secures the return of 'clockwork regularity.'

Wyeth

JOHN WYETH & BROTHER LTD.
Clifton House · Euston Road · N.W.1

'PETROLAGAR'
Trade Mark
EMULSION

The Original and Standard Emulsion of Petroleum

Angier's Emulsion is made with petroleum specially purified for internal use. It is the original petroleum emulsion — the result of many years of careful research and experiment. There is a vast amount of evidence of the most positive character proving the efficacy of Angier's in sub-acute and chronic bronchitis. It not only relieves the cough, facilitates expectoration, but it likewise improves nutrition and effectually overcomes the constitutional debility so frequently associated with these cases. Bronchial patients are nearly always pleased with this emulsion, and often comment upon its soothing, "comforting" effects.

Angier's Emulsion

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ANTABUSE

PURE TETRAETHYLTHIURAM DISULPHIDE

for peroral administration in the treatment of
CHRONIC ALCOHOLISM

The bibliography concerning this product is very considerable. Full details, and literature on application

Packings of 25 & 50 Tablets 0.5 gm.
Sole distributers for U.K. and N. Ireland

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UNIQUE PSYCHOLOGICAL APPROACH
NO SECONDARY ACID RISE
EFFECTIVE SEDATION
NO CO_2 FORMATION

PROLONGED NEUTRALISATION
ANTI-VAGAL ACTION
NO ALKALOSIS
NO CONSTIPATION

Ask your Chemist
about
VENTRALKIA

PROVIDING FOR THE FIRST TIME APPROPRIATE FFFECTIVE TREATMENT FOR ALL STAGES OF PEPTIC ULCER IN A SINGLE TABLET

Simply prescribe "Ventralkia A m. 21 tabs sig i tds" followed by 'B' & 'C' in weekly turns

ONLY AVAILABLE ON PRESCRIPTION

FORSTERS (Pharmaceuticals) Ltd. Manufacturing Chemists, Seaham

CLINITEST—urine-sugar analysis set

TRADE MARK

Distinct colours for reliable readings

Doctors and patients can be sure of the reliability and simplicity of 'Clinitest' (Brand) Sets and Reagent Tablets. The most distinct colour scale, the easily recognisable colours of the test, give patients confidence in their readings, so reducing the number of unnecessary visits to doctors. This one-minute, no heating, copper reduction tablet test can be made easily even under travelling conditions.

A valuable instrument for the practitioner for routine sugar analysis, 'Clinitest' is the accepted test for the detection and control of glycosuria. Sets and refill bottles of tablets comply with official specifications for appliances and reagents which may be prescribed on form E.C.10.

CLINITEST 36

Approved by the Medical Advisory Committee of the Diabetic Association

Complete Set, including 36 tablets . . . 10/-
Refill bottles (36 tablets) 3/6

Supplies always available at your chemist. Medical literature available on request to the sole distributors

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Manufactured by Miles Laboratories Ltd., Bridgend, South Wales, under licence from Ames Company, Inc.

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"CELLANBAND"

ZINC PASTE BANDAGE

B.P.C./N.H.S.

4 inches × 7 yards

A ventilated dressing of the Unna's Paste type, which will allow the escape of free exudation and thus prevent development of troublesome dermatitis. Indicated for Varicose Ulcers, Phlebitis, Lymphangitis and in certain orthopædic cases.

For your prescriptions

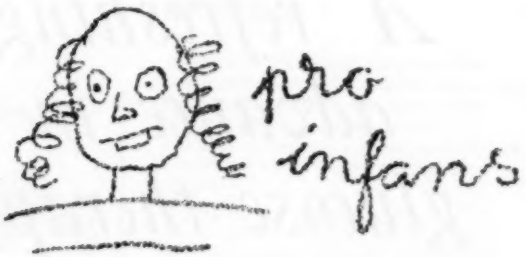
Recognized as a very successful treatment of varicose conditions of the leg. They are also indicated for Strains, Fractures and general orthopædic cases.

"VARIBAN"

ELASTIC ADHESIVE BANDAGE

B.P.C./N.H.S.

PRODUCTS OF *Cuxson Gerrard & Co. Ltd.* OLDBURY, BIRMINGHAM



CO-OPERATION is quickly established between young patient and doctor when GLUCOVITE is the tonic prescribed.

Its delicious flavour and attractive appearance are universally popular with children (and, it might not be out of place to say, with adults, too!).

Adherence to the dosage time-table, so important in tonic therapy, thus presents no problem.

GLUCOVITE combines vitamins A & D with glycerophosphates of manganese, sodium and potassium and ferric pyrophosphate in a deliciously palatable elixir. It has long been a firm favourite with doctors who have experienced its high acceptability and therapeutic effectiveness.

Clinical samples and literature gladly, on request.

GLUCOVITE

TONIC ELIXIR

Vitamins A & D with glycerophosphates and iron.

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A refreshing advance in glucose therapy

The problem of presenting medicinal glucose in a tempting form has been solved in LUCOZADE. This glucose-containing beverage is so delightful, and refreshing, that it is readily acceptable to the most reluctant invalid palate. Sick children, especially, love LUCOZADE.

Containing Dextrose, Maltose and Dextrin in solution equivalent to 23% w/v Liquid Glucose B.P.

LUCOZADE

An improved form of glucose therapy

LUCOZADE LTD · GT. WEST ROAD · BRENTFORD · MIDDX.

royds Spec. 1

Lifelessness

APATHY or lifelessness are symptoms commonly observed in debility states, but despite clinical tests, the cause often remains obscure. These are the circumstances in which the possibility of conditioned B-avitaminosis may be considered.

A preparation containing all the elements of the B-Complex as present in yeast extract, 'BEPLEX' will speedily resolve doubts on the vitamin aetiology of symptoms, and restore any deficiencies that have arisen.

Wyeth

'Beplex'
Trade Mark
ELIXIR and CAPSULES

JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1

Bioglan

VITA-E 75 I.U.

GELUCAPS

(Vitamin E)

in the treatment of

Cardiovascular-Renal Diseases

Each Gelucap contains a concentrate of natural esters (d,alpha-tocopherol acetate) from vegetable oils, type VI, equivalent to 75 mgm. d.l. alpha-tocopheryl acetate).

This therapy is today extensively prescribed in the U.K.

Also available a complete range of endocrine and endocrine-vitamin preparations including BIOGLAN-A/R capsules for rheumatism, arthritis, rheumatoid-arthritis and fibrositis (based on the same cortical principle as CORTISONE and ACTH).

THE BIOGLAN LABORATORIES LTD., HERTFORD, HERTS.

Tel. Address: "BIOGLAN TOLMERS" ***Literature on request*** Phone: CUFFLEY 211

GUTTILIN

Automatic Dropper Tube

(BENGUÉ PATENT)

The Ideal Container and Dropper for Ophthalmic, Aural and Nasal Drop Medication

This glass tube prevents contamination of the solution, maintains its stability and therapeutic action indefinitely and facilitates the application drop by drop.

A comprehensive range of solutions of recognised medicaments in accepted strengths is available.

Solutions in Guttilin Tubes require no sterilization before use, are most convenient to the Practitioner, and also to Patients for personal application of drops when prescribed by the Physician.

List of solutions on request

BENGUÉ & CO. LTD., Manufacturing Chemists

MOUNT PLEASANT, ALPERTON, WEMBLEY, MDDX.

INCRETONE

With VITAMIN B_1

Stomachic and Tonic Augmented by Vitamin B_1

Incretone is a general tonic to which Vitamin B_1 has been added. The vehicle contains glandular substances pituitary and gonads and the bitter tonic principles taraxacum and gentian.

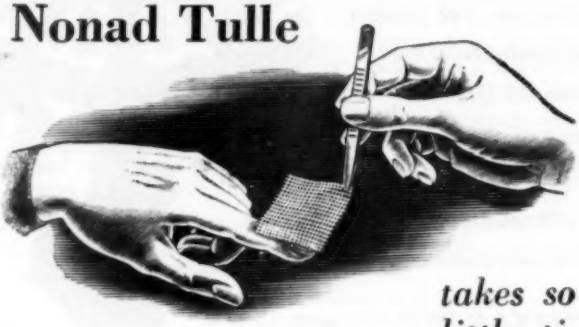
Indicated in the treatment of anorexia, asthenia and general debility, and is a splendid aid in the convalescent period.

Supplied in bottles of 6 ounces

G. W. CARNRICK CO.

Distributors: Brooks & Warburton, Ltd., 232-242 Vauxhall Bridge Road, London, S.W.1 Tel. Vic. 1282

Penicillin Nonad Tulle



takes so little time

for, in a matter of seconds, it can be applied as a primary dressing round the finger following incision of a septic focus.

No need to prepare a dressing of penicillin ointment and gauze, no need to cut the dressing to the right size, Penicillin Nonad Tulle is designed in several sizes to suit a variety of requirements and the pieces 2 inches by 2 inches are a convenient size for use as a finger dressing.

Penicillin Nonad Tulle is the ideal bacteriostatic dressing to be applied to wounds infected with penicillin-sensitive organisms. The wide-mesh gauze is impregnated with an emulsifying base containing 1,000 i.u. of penicillin per gramme. The non-adhesive nature of the tulle encourages the formation of granulation tissue and ensures the easy removal of the gauze without disturbance of the newly formed tissue.

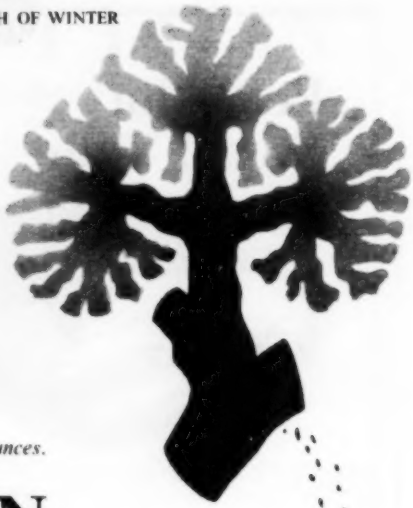
Penicillin Nonad Tulle is effective and easy to apply.

PENICILLIN NONAD TULLE

In tins, containing 10 pieces each 4″×4″ or 40 pieces each 2″×2″

ALLEN & HANBURYS LTD · LONDON · E·2

AUTUMN AND THE APPROACH OF WINTER herald an increased incidence of bronchitis, colds, laryngitis and tracheitis. These and other irritative and congested conditions of the respiratory tract call for 'Benylin Expectorant'—a rational and effective preparation for the relief of unbeneficial cough associated with such conditions.



Supplied in bottles of 4, 16 *and* 80 *fluid ounces.*

BENYLIN®

EXPECTORANT

® REGISTERED TRADE MARK

PARKE, DAVIS & COMPANY, LIMITED

HOUNSLOW · MIDDLESEX *Inc. U.S.A.*

In conditions affecting the Pulmonary Organs

"EUPNINE VERNADE"

Eupnine Vernade is a solution containing 10 per cent. of caffeine iodide. The active substance is dissolved in a special medium, the composition of which fulfils several essential conditions. It ensures complete stability of the caffeine salt ; it increases the patient's tolerance to the drug, and it makes it more palatable.

A condition which affects the pulmonary organs cannot, in its treatment, be dissociated from consideration of cardiac strain and the possibility of renal insufficiency. An efficient therapy must be one which attempts to treat all these aspects.

INDICATIONS : Asthma, Hay-Fever, Bronchitis, Emphysema, etc., etc.

DOSAGE : Teaspoonful in a little liquid two or three times a day before meals. Children : Proportionate to weight.

Literature and clinical samples free on request

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ADVANCES IN MEDICAL TREATMENT

The contribution of British Schering to the advance of medicine during the last two years

ENTEROCID (Phthalylsulphacetamide) **TABLETS AND SUSPENSION** *For the treatment of bacillary infections of the intestinal tract.*	**A non-systemic sulphonamide which attains a high concentration in the tissues of the bowel wall.**	**IVIRON** (Sterile solution of saccharated iron) *For the rapid restoration of haemoglobin in iron-deficiency anaemia.*	**A solution of very low toxicity for intravenous injection in cases where oral iron is contraindicated or a rapid response is required.**
MALIDONE (Allylmethyloxazolidinedione) *For the oral treatment of the petit mal syndrome*	**An anticonvulsant of high therapeutic activity and few side effects. Does not cause photophobia.**	**MERCAZOLE** (1-methyl-2-mercaptoimidazole) *For the control of hyperthyroidism and thyrotoxicosis*	**A new, potent, oral antithyroid preparation of low toxicity and high therapeutic index.**

Samples and further information on all these preparations will gladly be sent on request

British Schering Limited

229-231 Kensington High Street, London, W.8, telephone WEstern 8111

SB41/51

MARMITE

yeast extract

in the treatment of

NUTRITIONAL MACROCYTIC ANÆMIA

Although its precise rôle is not yet understood, Marmite has long been known to be effective in the treatment of certain types of anæmia, for example, nutritional macrocytic anæmia, and the macrocytic anæmias of pregnancy and of coeliac disease.

Marmite contains riboflavin (1.5 mg. per oz.) and nicotinic acid (16.5 mg. per oz.) as well as an unidentified hæmopoietic principle. Among the other vitamins which have been determined in Marmite are folic acid, pyridoxin, pantothenic acid, biotin, choline, and inositol.

Obtainable from Chemists and Grocers

Special terms for packs for hospitals, welfare centres and schools

Literature on application

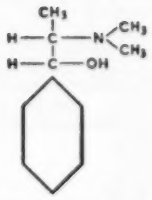
THE MARMITE FOOD EXTRACT CO., LTD. 35 Seething Lane, London, E.C.3

5104

METHEPH

Methylephedrine Hydrochloride

for the Control of Enuresis



l-N-Methylephedrine

'Metheph'-Regd. Trade Mark

When normal physical control of the bladder is defective, uninhibited reflex contraction can often be suppressed by 'Metheph,' and full control of enuresis in children secured in 3 to 4 weeks.

The action of 'Metheph' is more prolonged than that of ephedrine, and it has fewer side-effects (*B.M.J.*, 1950, Nov. 11, 'Enuresis').

The average dose required is one tablet (2/3 grain) at bedtime for children of 3 to 6 years, and 1½ to 2 tablets for older children.

'Metheph' is also of great value in the relief of bronchial spasm and for the prevention of asthmatic relapses.

'Metheph' is issued in tablets (2/3 grain), in bottles of 25, 100, and 500.

Freely prescribable under the N.H.S. Scheme

Literature available on request

MOORE MEDICINAL PRODUCTS LTD

ABERDEEN LONDON OFFICE: 64 GLOUCESTER PLACE, W.1 LONDON

WELBECK 5718

modern
treatment of
varicose conditions

Modern technique embraces ligature, injection and firm compression bandaging

Suitable compression bandages are:

Elastoplast Elastocrepe
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Viscopaste Ichthopaste
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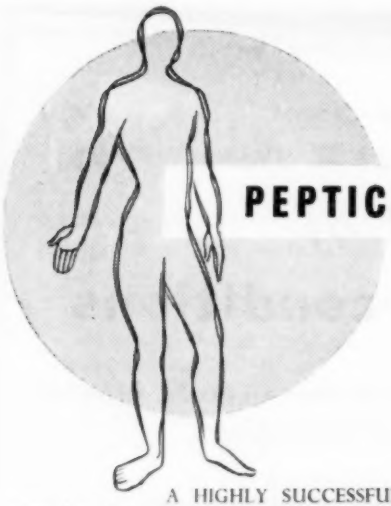
(*Plentiful supplies of all these bandages are now available*)

Products of T. J. SMITH & NEPHEW LTD., NEPTUNE ST., HULL



PEPTIC ULCER THERAPY

An aetiological approach

A HIGHLY SUCCESSFUL TREATMENT which for over seven years has been used in clinics and hospitals in several countries in cases of peptic ulcer consists of the administration of gastro-intestinal tissue extract. Hundreds of patients, including ambulatory cases, have benefited from this form of substitution therapy which provides the substances lacking in the stomach and duodenum in peptic ulcer.

The extract used in this treatment—after extensive tests in the laboratory and clinical practice—was introduced in 1944 under the name ROBADEN. Reports of its value in peptic ulcer—including ambulatory cases—are now being further confirmed—as supplies become more easily available in this country—by similar experiences of physicians here.

ROBADEN is particularly useful in ambulatory cases and symptomatic improvement is often evident after the first few injections. The treatment consists in the use of both ampoules and tablets. The ampoules are supplied in separate form for gastric and duodenal ulcers. Full details and clinical references on request.

ROBADEN

PRODUCT OF ROBAPHARM LTD.

The Robaden trade mark is the property of Robapharm Laboratories, Basle, Switzerland, manufacturers of biological specialities to the medical profession.

Distributors in the United Kingdom and Eire:

WARD, BLENKINSOP & CO., LTD.

6, HENRIETTA PLACE, LONDON, W.1

Telephone: Langham 3185

The first step in all Nervous Affections —

ELIXIR GABAIL

This distinctive product has won a place in the treatment of all types of nervous affections by reason of its achievement of a high concentration of VALERIAN with none of the disagreeable and nauseating features which so often invalidate the outstanding therapeutic qualities of the drug. Reinforced with minimal doses of strontium bromide and chloral hydrate, ELIXIR GABAIL has no counterpart in modern practice for the achievement of sedation without recourse to barbiturates or narcotics.

Dosage: One tablespoonful in water twice or thrice daily. *For Insomnia:* Two tablespoonfuls at bedtime.

GABAIL

Supplied in bottles of 187 c.c., 16oz., and in bulk for dispensing and hospital use.

Literature and Sample from the Distributors:

THE ANGLO-FRENCH DRUG CO., LTD. 11-12 Guilford Street, London, W.C.1

ANGINA PECTORIS

BRONCHIAL ASTHMA

CARDIAC OEDEMA

CHEYNE-STOKES RESPIRATION

ACUTE PULMONARY OEDEMA

Cardophylin

A preparation of established value as a dilator of the bronchi, the renal vessels and the coronary arteries.

CARDOPHYLIN *is presented in :—*

Tablets, each containing 0.1 gm.

Suppositories, each containing 0.36 gm.

Ampoules, for intramuscular injection containing 0.48 gm.

Ampoules, for intravenous injection containing 0.24 gm.

Cardophylin is the registered trade mark of the manufacturers Whiffen & Sons Ltd.

Literature is available on request to the distributors :—

BENGER LABORATORIES LTD., HOLMES CHAPEL, CHESHIRE. TELEPHONE 3112

Spirella INDIVIDUAL CORSETRY SERVICE

For the More Ample Figure

Obtainable through Resident Spirella Corsetieres everywhere. For addresses see Spirella page in the Telephone Directory . . . or on application to

The
SPIRELLA COMPANY *of* GT. BRITAIN LIMITED
LETCHWORTH HERTS . TEL : LETCHWORTH 159
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A case for the Surgeon

Here are the world's finest scalpels & handles packed in a neat, tastefully designed plastic case that is compact, easy to use and which meets the strict standards of hygiene and aesthetics of the modern operating theatre. Contains 3 different handles and 6 dozen blades in 9 shapes, as illustrated.

Swann-Morton

Details from
W. R. SWANN & CO. LTD.
PENN WORKS · SHEFFIELD · 6

ULCER CHARACTERISTICS

Deep Naso-Labial Groove

Clinicians have repeatedly noted a similarity of facies in patients suffering from peptic ulcer, the outward signs of an inward worrying character part cause and part effect of the ulcer. The deep naso-labial groove or furrow is an example of one of the features commonly seen in these cases. While by itself of no diagnostic significance it is nevertheless an interesting little link in the chain of evidence that leads from suspicion to certainty. A more reliable characteristic of the ulcer patient is amenability to 'ALUDROX' therapy.

'ALUDROX' FOR PEPTIC ULCER

For the treatment of peptic ulcer 'ALUDROX' has advantages now fully appreciated by the medical profession.

* Buffers gastric acid.
* Inactivates pepsin.
* No acid rebound.
* No fear of alkalosis.
* Allows normal digestion to proceed.

'Aludrox'

Trade Mark

Wyeth JOHN WYETH & BROTHER LTD., CLIFTON HOUSE, EUSTON ROAD, N.W.1

A Superior Antihistaminic Preparation

EFFECTIVE. Diatrin* provides the physician with an effective means for the prompt relief of allergic symptoms caused by the liberation of histamine in the tissues.

MINIMUM SIDE-EFFECTS. Unpleasant side-effects such as drowsiness, lethargy, vertigo, nausea, and vomiting are rarely encountered when Diatrin is administered.

LOW TOXICITY. In toxicity studies, Diatrin has been found to be approximately one-half to three times less toxic than other antihistaminic substances.

INDICATIONS . . . Urticaria, particularly the acute form; Hay fever; Allergic vasomotor rhinitis; Atopic eczema and dermatitis; Contact dermatitis; Neurodermatitis; Drug rashes (penicillin etc.); Pruritus; Erythema multiforme; Vernal conjunctivitis.

FORMULA. N, N-dimethyl-N'-phenyl-N' - (2-thienylmethyl) - ethylenediamine monohydrochloride.

DIATRIN

Available in sugar-coated oral tablets, 50 mg. each—bottles of 20 and 250.

NO WARNER PREPARATION HAS EVER BEEN ADVERTISED TO THE PUBLIC

William R. WARNER *and Co. Ltd. Power Road, London W.4.*

A SYMBOL IS MORE THAN A SIGN

To the psychologist a symbol is not merely a static sign but a dynamic experience. Similarly, to the clinician the symbol "A.B." portrays far more than can be expressed in rational words. The preference for Insulin A.B. in all parts of the world is based on trust and experience—on the knowledge that the mark "A.B." signifies all that can be desired in quality and performance.

INSULIN A.B.

INSULIN A.B.
Globin Insulin (with zinc) A.B.
Protamine Zinc Insulin A.B.

Joint Licensees and Manufacturers:
ALLEN & HANBURYS LTD. : THE BRITISH DRUG HOUSES LTD.

● **COMMON COLD**

"..a few days in bed ..."

Excellent advice for those who can afford it, the problem has been to find an effective therapeutic agent suitable for the ambulant case.

In a carefully controlled trial on ambulant patients, the most effective preparation was a combination of codeine and papaverine giving improvement or recovery in 75% cases of incipient colds in 24-48 hours (*J. Amer. Med. Ass.*, 1933, **101**, 2042). This has been confirmed by other workers.

ACORZA LIQUIDUM incorporates this effective combination and the dosage recommended on each vial follows that so successfully employed above.

ONE SIZE ONLY (23 CCS.) SUFFICIENT FOR ONE TREATMENT

ACORZA LIQUIDUM

FREELY PRESCRIBABLE UNDER N.H.S.

FORSTERS (Pharmaceuticals) Ltd. *Manufacturing Chemists,* **Seaham**

THE year just ending has seen a remarkable step forward in the adoption, following adequate clinical tests, of F "99" in the treatment of intractable skin disorders. This reinforces similar experience on the Continent where F "99" has been extensively and successfully prescribed for a number of years. It has been established beyond doubt that certain skin disorders have their origin or aggravating factor in a deficiency in the system of essential unsaturated fatty acids. Until recently the unsaturated fatty acids could be used in medicine only in a limited way, as the preparations available had neither a sufficient purity nor a standardised biological activity.

Standard Biological Activity

F "99" is the first product containing linoleic and linolenic acids to a degree of 99.5 per cent. purity and with a biological activity standardised at 340,000 to 350,000 Shepherd-Linn units per gramme, a figure never previously approached. The remarkable clinical results obtained show the extreme importance of the degree of purity and of the biological activity of the unsaturated fatty acids used in medicine.

Composition

The biologically active concentrate used in F "99" is made exclusively from vegetable oils and contains the following proportions of the unsaturated fatty acids—

Linoleic Acid	..	$C_{18}H_{32}O_2$	2/3
Linolenic Acid	..	$C_{18}H_{30}O_2$	1/3

Therapeutic Indications

F "99" is indicated in cases of Eczema, Infantile Eczema, Furunculosis, Varicose Leg Ulcers and Acne Rosacea, especially those of long standing. No secondary or undesirable effect of any kind is to be feared. Physicians, pharmacists and dispensers should investigate the convincing clinical evidence furnished for F "99". Professional literature, copiously illustrated with medically attested photographs and research literature references is available on request from:

INTERNATIONAL LABORATORIES, LTD.

Dept. P.R., 18 Old Town, London, S.W.4. *Telephone:* MACaulay 3481.

Urolucosil*

A SULPHONAMIDE
FREE FROM SIDE-EFFECTS

One of the most valuable characteristics of Urolucosil is the remarkable absence of side-effects noted with this sulphonamide. Such conditions as cyanosis, vomiting, acidosis, hypersensitivity, have yet to be reported; it is most uncommon for there to be any upset of the blood picture or disturbance of the intestinal flora with Urolucosil. Because Urolucosil is a compound with the high solubility of 98% at a pH of 7, it is unlikely that any blockage of the urinary passage by crystalline deposits will be caused; no diminishing of urinary output caused by such blockage has in fact been reported since Urolucosil was introduced to the medical profession in Great Britain. Finally, depression, which so often militates against the well-being of a patient, is virtually absent when Urolucosil is prescribed.

Urolucosil is especially indicated in uncomplicated infections due to B.coli and other organisms of the coliform group: acute cystitis, acute pyelitis, pyelitis of pregnancy: urinary tract infections in children: neurogenic bladder.

Each tablet of 0·1G contains:
2-sulphanilamido-5 methyl-1-thio-3: 4-diazole.

Urolucosil
A TRADE MARK

Packed in bottles of 25 0·1G. tablets and 250 0·1G. tablets. Part I., S.I, S.IV Poison, not subject to purchase tax.

NO WARNER PREPARATION HAS EVER BEEN ADVERTISED TO THE PUBLIC

William R. **WARNER** *and Co. Ltd. Power Road, London W.4.*

An Effective Antacid

of established value

Immediate neutralization of gastric acid, yet unaccompanied by the disadvantages arising from carbonate medication, clearly indicates the clinical superiority of 'Milk of Magnesia'* as a therapeutic antacid.

Non-systemic in action, 'Milk of Magnesia' may confidently be prescribed in a wide variety of conditions associated with gastric acid disturbance—from the mild case of dyspepsia to the acute ulcer stage—where intensive alkaline treatment is essential.

'Milk of Magnesia' reacts with the acids of the stomach to form a neutral laxative salt which promotes gentle but effective elimination.

'Milk of Magnesia'

REGD.

ANTACID LAXATIVE

The Chas. H. Phillips Chemical Co. Ltd.

1, WARPLE WAY, LONDON, W.3.

* *'Milk of Magnesia' is the trade mark of Phillips' preparation of magnesia.*

'Benzedrine' Inhaler...

for children's colds

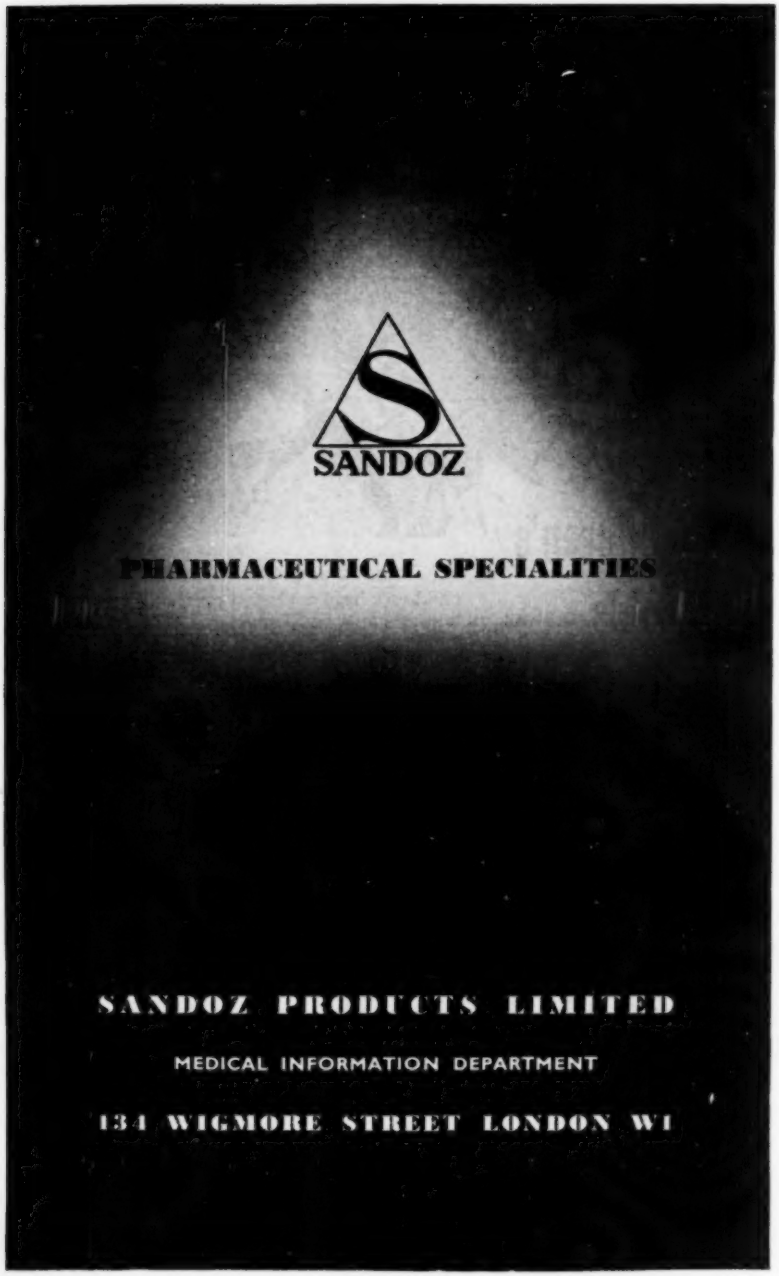
In prescribing 'Benzedrine' Inhaler for children's head colds you prescribe a remedy which will prove of constant service throughout the winter months. Children welcome the novelty of 'Benzedrine' Inhaler treatment and if the Inhaler is used at the first sign of a cold, nasal congestion will be reduced and the patency of the nasal passages will be maintained. 'Benzedrine' vapour has no deleterious effect on the delicate cilia of the nose, and since it is volatile it penetrates to areas usually inaccessible to liquid inhalants. Even in very young children, over stimulation and other undesirable reactions do not occur with proper dosage. With children, an adult should supervise the use of the Inhaler and retain possession of the tube.

'Benzedrine' Inhaler

A VOLATILE VASOCONSTRICTOR

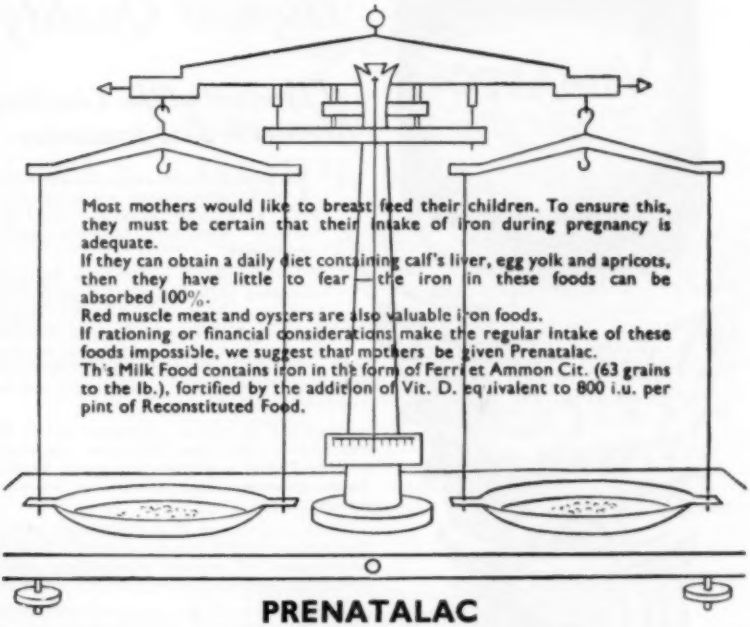
MENLEY & JAMES, LIMITED, 123 COLDHARBOUR LANE, LONDON, S.E.5
for Smith Kline & French International Co., owner of the trade mark 'Benzedrine'

L1P91


SANDOZ
PHARMACEUTICAL SPECIALITIES
SANDOZ PRODUCTS LIMITED
MEDICAL INFORMATION DEPARTMENT
134 WIGMORE STREET LONDON W1

IRON is worth its weight in GOLD

during pregnancy



Most mothers would like to breast feed their children. To ensure this, they must be certain that their intake of iron during pregnancy is adequate.

If they can obtain a daily diet containing calf's liver, egg yolk and apricots, then they have little to fear — the iron in these foods can be absorbed 100%.

Red muscle meat and oysters are also valuable iron foods.

If rationing or financial considerations make the regular intake of these foods impossible, we suggest that mothers be given Prenatalac.

This Milk Food contains iron in the form of Ferriet Ammon Cit. (63 grains to the lb.), fortified by the addition of Vit. D. equivalent to 800 i.u. per pint of Reconstituted Food.

PRENATALAC

ANALYSIS

	Dry Food	Reconstituted Food (1 in 8)
Fat	27.1%	3.4%
Protein	26.5%	3.3%
Lactose	37.5%	4.7%
Milk Salts	5.8%	0.7%
Iron Ammonium Citrate	0.9%	0.1%
Moisture	2.2%	87.8%

		Dry Food	Reconstituted Food (1 in 8)
Calorific Value	per oz.	145	18.1
	per 100 grms.	514	64.3
Vitamin D.	per oz.	320 i.u.	
	per pint		800 i.u.
Calcium	per oz.	230 mgms.	
Phosphorus	per oz.	175 mgms.	
Iron	per oz.	50 mgms.	

COW & GATE MILK FOODS

Cow & Gate Ltd., Guildford, Surrey

4820

A Delicious, Concentrated, Vitamin Food of the Highest Quality

A Product of the Ovaltine Research Laboratories

TO the physician requiring a product which incorporates important vitamins in a form acceptable to every patient, 'Vimaltol' presents special advantages.

'Vimaltol' is made from specially prepared malt extract of high protein content, yeast—one of the richest sources of vitamin B—and Halibut Liver Oil, an important source of vitamins A and D. It is also fortified with additional vitamins and mineral salts, and has a delicious orange flavour.

'Vimaltol' is thus an important aid in the treatment of the many abnormal conditions resulting from the deficiency of one or more of the essential vitamins in the average everyday dietary.

The routine use of 'Vimaltol' helps normal development of the growing organism and the maintenance of correct metabolism, while raising the general resistance against infection.

'Vimaltol' has thus a very wide application in general practice for patients of all ages. It can be prescribed with advantage at all seasons.

The Ovaline Factory in a Country Garden

M.341

CHEMOTHERAPY OF TUBERCULOSIS

Aminacyl
WANDER
Granulate

Adds a New Quality to
P.A.S. CALCIUM SALT Presentation

THE ONLY JUSTIFICATION for the introduction of a newer form of an already accepted tuberculostatic drug is its ability to provide additional worthwhile qualities, for example: greater convenience of dispensing, higher acceptability to patients and extra therapeutic advantage.

'Aminacyl' Granulate is a highly concentrated form of P.A.S., containing about 85% anhydrous Calcium Aminosalicylate—the latest salt to undergo successful trial—and providing the equivalent of 75% free acid P.A.S. and 9.8% calcium. Its superiority in the chemotherapeutic management of tuberculous disease is characterized by these qualities:—

CONVENIENCE *To Pharmacists* 'Aminacyl' Granulate is processed to ensure against any possibility of deterioration.
'Aminacyl' Granulate obviates the nuisance of preparing aqueous or syrupy solutions.
To Patients 'Aminacyl' Granulate is thoroughly acceptable to patients of all ages and throat types.
To Doctors 'Aminacyl' Granulate permits the physician to order any fractionated dosage; there is no "tie down" to large multiples of grammes.

STABILITY . . . 'Aminacyl' Granulate cannot deteriorate on standing over many months.

LIBERATION . . 'Aminacyl' Granulate is sialoresistant-coated to ensure that the distasteful contents are freed only after swallowing.

WALLING-OFF 'Aminacyl' Granulate in approximately daily dosage (12 to 15 gm.) provides 1.4 gm. of calcium in assimilable form to assist "walling-off" pulmonary foci. This therapeutic advantage is not permitted with Sodium P.A.S.

MODE OF ADMINISTRATION

'Aminacyl' Granulate provides effective therapeutic blood levels when administered in daily divided dosage of 12 to 15 gm. as 2 level teaspoonfuls of the Granulate (= 4 gm. free acid P.A.S.) thrice daily.

Literature and further information gladly sent on physicians' request to the Medical Dept.

PRESENTATION

Package for one week	100 gm.
Package for one month	400 gm.
Dispensing Package	2,000 gm.

A dosage measure (capacity 2 gm. approx.) supplied gratis with each package.
'Aminacyl' brand of Calcium P.A.S. is also supplied in bulk powder form.

A. WANDER, 42 Upper Grosvenor St., Grosvenor Square, London W.1.

M.366

Ousting Superstition

MANY were the superstitious rites of early medicine. None, perhaps, was stranger than the ritual used in gathering black hellebore, the Christmas Rose. To potentiate its virtues as a cure for madness, those who sought it went barefooted, robed in white. Bread and wine were sacrificed. The right hand plucked the blossom and secretly conveyed it to the left.

Today, medicinal plants are cultivated by strictly scientific methods. The Wellcome Materia Medica Farms, for instance, are recognised as models of progressive husbandry—as thoroughly attuned to modern medical needs as, in their wider spheres, are the Wellcome Chemical Works and The Wellcome Research Laboratories. All these units of The Wellcome Foundation—pioneers in the development and production of synthetic drugs no less than of vegetable—work together for the furtherance of modern medical science. The many therapeutic agents they produce are distributed by . . .

BURROUGHS WELLCOME & CO.

(THE WELLCOME FOUNDATION LTD.) LONDON

GLANOID

PROETHRON

2 U.S.P. units per ml.

★ Increased strength

PROETHRON FORTE

4 U.S.P. units per ml.

Crude Liver Extracts for intramuscular injection

PROETHRON 15

NEW STRENGTH

15 U.S.P. units per ml.

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THE PRACTITIONER

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THE MONTH

Our Thousandth Issue

'We are on the threshold of still greater achievement'. On this optimistic note Mr. Charles Read concludes his article on 'advances in obstetrics and gynæcology', and his optimism is shared by other contributors to this Special Number. Professor R. H. Freyberg, for instance, in reviewing the present status of cortisone, considers that 'search for the knowledge on which to base a more satisfactory and practical treatment programme is going forward, stimulated by the fact that never before has this search been so hot on the trail of success'. The true significance of this optimistic outlook in therapeutics can only be appreciated by comparing the state of affairs revealed in this, our thousandth issue, with that which existed when our first issue was published—in 1868. In the interval the face of medicine has changed completely so far as therapy is concerned, and yet there is every reason to believe that equally dramatic changes may occur within the next generation. Whilst it would be foolish to decry these advances and suggest, as some have done (and not altogether without reason) that the 'advances' are often more apparent than real, it is necessary for us as doctors to protect our patients from unjustifiable optimism. The dangers involved are well summarized by Sir Henry Cohen, in his article on 'advances in medicine', and his wise words of warning require careful consideration by every practitioner, whether in consulting or general practice: 'It is imperative to stress once again that although the public is rightly entitled to receive the benefits of new discoveries as early as possible, they should not be exposed to the risks of being the victims of uncritical enthusiasms, nor of inadequately tested remedies, which may carry serious hazards'.

What You Fancy

The systematization of the culinary and gastronomic arts has provided more pitfalls for the unwary scientist than almost any other branch of applied science. The accumulated experience of the centuries has seldom been proved wrong, and the mere fact that the delicacies of the table can now be accurately, if unæsthetically, clothed in terms of calories, proteins, carbohydrates and fats, has got us very little farther in an understanding of the whims of the appetite. Even the apparently straightforward problem of obesity, with its deceptively simple formula of intake > output = gain in weight, is still awaiting final solution. Perhaps the most interesting recent incursion of the nutritionists into practical dietetics has been the story of phytic acid in relationship to rickets. It was in the early 1920's that Sir Edward Mellanby demonstrated in puppies the rickets-producing propensities of oatmeal, which he attributed to

the inhibitory action of the phytic acid in oatmeal upon absorption of calcium from the gut. On more than one occasion subsequently he has uttered a warning against the dire consequences this might have upon human welfare: 'Apart from extreme malnutrition, it would appear not improbable that in this country [i.e Great Britain], where the average diet is deficient in or contains a borderline quantity of antirachitic vitamin and calcium, and where sunshine is negligible, the ingestion of oatmeal during pregnancy and lactation of women, and in growing children, does much harm'. In spite of this scientific onslaught the Scots refused to give up their national dish, and a worker in South Africa has now come to their aid. In a penetrating analysis of all the available data, clinical, dietetic and scientific, A. R. P. Walker of the South African Institute of Medical Research (*Lancet*, 1951, **ii,** 244) has shown that there is no convincing evidence to suggest, far less prove, that, in this particular instance, the results of animal experiments are applicable to man. His analysis ranges over the writings of the older clinicians and the evidence from Scotland, Ireland, and tropical and semitropical countries. Of Scotland, for instance, he says: 'In Scotland, when the national diet contained a large amount of phytic acid and probably little calcium and vitamin D, it has not been established that rickets was widespread'. He sums up the position with a fairness and balance which can be commended to all workers in this difficult field: 'Since cereals and their products are of such profound importance in human nutrition, it seems reasonable to insist that any nutritional stigma attached to their consumption should be based on conclusive evidence. From the evidence discussed here it appears that the importance of phytic acid as an anticalcifying factor in human nutrition has not been established'.

'The Chloroform Myth'

Among the greatest advances in medicine during the last hundred years have been those achieved in the field of anæsthesia. Surgeons are among the first to admit that the dramatic developments in thoracic surgery and neurosurgery have only been possible because of the advances in chemotherapy and anæsthesia. Without these, no amount of surgical skill would allow of the successful carrying out of the modern operations on the heart, lungs and brain. The attention which these advances have rightly received, particularly in the fields of intravenous anæsthesia and muscle relaxants, has tended to obscure the fact that their increasing complexity renders them correspondingly difficult to perform. Where fully trained anæsthetists are available, as in the larger hospitals, this aspect of the problem is of no significance, as the patient receives the full benefit of modern anæsthesia without any increased risk. What is overlooked, however, is that a certain amount of surgery, both minor and major, must always be carried out under rather more primitive conditions and therefore by men who are not justified in using these elaborate procedures of the expert anæsthetist. Indeed, it is almost truer of anæsthesia than of any other branch of medicine that we are,

in the words of an American anæsthetist, 'too prone to regard as progress the complication of a once simple process'. It is undoubtedly this increasing awareness of the danger of misuse of modern anæsthetic techniques that is, in part at least, responsible for an editorial in *Current Researches in Anesthesia and Analgesia* (July-August 1951, **30**, 240) with the challenging title of 'The Chloroform Myth'. In this, Dr. Howard Dittrick, the directing editor, draws attention to a report on chloroform from the anæsthetists at the University of Wisconsin; 'It appears now that fear and mistrust of this drug have been based upon incomplete knowledge and misconceptions out of all proportion to the facts'. Dr. Dittrick concludes by contending that 'investigation should be continued in other clinics, especially in an endeavour to find one or more other drugs which may be used with chloroform to counteract any of its harmful reactions'. Coming so relatively soon after the centenary of the introduction of chloroform, this plea from the United States for its reconsideration has an increased piquancy. This is by no means diminished by the fact that the distinguished holder of the J. Y. Simpson Readership in the University of Edinburgh, who contributes the authoritative review of 'recent advances in anæsthesia' elsewhere in this issue (p. 418), should be such a staunch advocate of the use of intravenous barbiturates by general practitioners. This, of course, is merely emphasizing the views he expressed in 1948 (*Anæsthesia*, **3**, 52): 'For minor surgery, the use of intravenous barbiturates must, even in general practice, have superseded to a very large extent the use of chloroform and other agents and there seems very little reason why suitable training in the former method should not be given to the student as a substitute for training in inhalational methods'. Where chloroform is concerned, it does look as if the wheel of fortune were turning, if not full circle, at least three-quarters circle.

In Arduis Fidelis

THE vicissitudes of the medical services of the British Army constitute one of the most characteristic examples of our national gift for bungling. It is difficult, for instance, for the present generation to realize that in the Peninsular War the Duke of Wellington refused to set aside military vehicles to transport casualties to hospital on the grounds that this would interfere with the mobility of his army. Yet, less than a century and a half later Viscount Mountbatten was able to promulgate orders in S.E.A.C. whereby it was an offence if commanding officers of units allowed the morbidity rate from malaria to exceed a given figure, and indeed one commander was relieved from duty because he had allowed his men to become ineffective through disease. The proud record of the Royal Army Medical Corps in the 1939-45 war is merely the culmination of a century-old struggle for adequate recognition and official backing, and the present moment is a particularly appropriate one for the appearance of a new history of the Corps ('Not Least In The Crusade', by Peter Lovegrove. Aldershot: Gale and Polden Ltd., price 5*s*., postage 6*d*. extra). This has been written primarily as the official textbook for the instruction of

junior officers and recruits in Corps history, but it deserves a wider public, not only among all those who have served in the Corps during both world wars, but also among the medical profession as a whole. It traces the history of the Army medical services from the earliest times to the jubilee of the Corps in 1948. There has been a tendency to criticize the Corps for not keeping abreast of the times. In this attractively written history Mr. Lovegrove makes it abundantly clear that time and again the fault lay in the higher levels at the War Office which refused the means, financial and otherwise, to allow the medical services to be maintained in peace time at the same high level as was expected of it in time of war. This short history tells a story of which the Corps has every reason to be proud.

Hotel Kitchen Hygiene

One of the disturbing features of the annual report of the Chief Medical Officer of the Ministry of Health, for 1949, which has just been published, is the reference to the great increase in outbreaks and cases of food poisoning which was reported during this year. As *The Times* points out, this is 'an outstanding example of a preventible disease which could be practically abolished by a concerted effort from all concerned with the handling of food'. As the representatives of the section of the profession most intimately concerned with this problem, the Society of Medical Officers of Health have been particularly active in taking steps to reduce this public health hazard. At a recent meeting of the council of the Society, a report was received of a meeting between representatives of the Society and of the Automobile Association (*Public Health*, July 1951, **64**, 200), at which the representatives of the former appealed for the cooperation of the A.A. and other motoring organizations in helping to maintain a high standard of hygiene in hotel kitchens. It was suggested that through their system of classification the A.A. could bring considerable influence to bear upon hotels so as to ensure that their kitchens and food arrangements reached a reasonable standard. Apparently there is an impression among medical officers of health that the surveyors of the A.A. do not pay the same attention to the kitchens and food storage arrangements as they do to public rooms. The response of the A.A. representatives was that, whilst they were in full agreement with the desirability of raising hotel standards, they were doubtful whether their organization could tackle this aspect of the problem. All who are members of the Automobile Association and the Royal Automobile Club will be interested in the statement of their representatives at this informal conference that the starring system is an indication not of quality but only of type of hotel. In the end the A.A. and R.A.C. representatives, impressed with the importance of the matter, agreed to investigate the possibility of their associations taking action along the lines suggested by the representatives of the medical officers of health. They can rest assured that they will receive the wholehearted backing of every member of their associations, and there can be little doubt that this backing will be shared by all intelligent hotel keepers.

THE CHANGING FACE OF MEDICINE 1868–1951

By SIR HENRY DALE, O.M., G.B.E., M.D., F.R.C.P., F.R.S.

MEDICINE in 1868 and in 1951: what a contrast! The change, of course, may be regarded as one aspect of a much wider one, involving the whole of the material basis of the civilization of advanced countries, and due to the progressive applications of scientific discovery. This change seems everywhere still to be continuing, with even a pronounced acceleration; and it is certainly obvious now in the case of medicine. If we look back, however, over the period under review, we must conclude, I think, that medicine came relatively late under the influence of this modern, scientific revolution. And this is the more remarkable, in view of the facts that medicine in ancient times had been regarded as one of the two main branches of scientific activity, and that the experimental method in science, then still a novelty, had been given its first practical applications in this country, early in the 17th century, by two physicians, Gilbert and Harvey. Of these, the latter had given to its potentialities, for the advancement of medical knowledge in particular, not only a first and triumphant demonstration, but his own fervent and life-long advocacy.

THE MIDDLE NINETIES

If we try to form a mental picture of what medicine had become by the middle of the 19th century, we cannot, I think, avoid the conclusion that it had largely escaped the influence of the great changes by which, since the middle of the 18th century, discovery and invention had been so rapidly transforming the general aspect of life in this country. The rapid expansion of the population and its crowding into new towns, for the service of newly mechanized and power-driven industries, had naturally created new problems of hygiene or, to speak more accurately, had brought old problems to light by the new scale of their concentration. For the effective handling of these problems medical knowledge was needed; but it was not yet available. It was a layman, Edwin Chadwick, Secretary to the Poor Law Commission, who first brought effectively to general notice the scandal of the horribly insanitary character of the housing and the common conditions of life available to the poorer classes in London. When medical adminstrators, such as Southwood Smith and John Simon, endeavoured to intervene with practical measures, based largely upon evidence of the association of water supplies contaminated by sewage with the spread of epidemic diseases, and particularly of cholera, they could offer no better explanation of the observed connexion than the 'contagia' long known to tradition. Simon, indeed, in his lectures on pathology, had recognized as early as 1850 that such a 'contagium' acts in inconceivably small doses, increases with great rapidity in

the infected body and, if recovery ensues, leaves behind it a specific immunity. This, however, was little more than Jenner already knew about one kind of contagium, half a century earlier; and it was, in fact, impossible to advance further without the direct experimental evidence which was to come some two decades later, after the ground had been prepared by Louis Pasteur's recognition of living and self-propagating organisms as responsible for various kinds of fermentation and putrefaction. Medicine had still to wait for this exact, experimentally controlled evidence, and to learn to use it when it came.

THE GROWTH OF SCIENCE

A recent writer (Charles Singer; 'Medicine' in *Chambers's Encyclopædia*), writing of the rise of modern physiology, suggests that 'the conclusions of Müller, Claude Bernard and Ludwig form the main scientific background of the clinical practice of our time. The movement they represent, together with the knowledge of the cellular structure of the body and of the life histories of disease-causing organisms, are the three main ideas which separate the physicians of the 20th century from Laennec and those of earlier times'. There may be room for some difference of opinion, as to whether these 'three main ideas' can be regarded as covering the whole range of the scientific knowledge which now contributes to the technical equipment, indeed, of the progressive physician, but also, and much more importantly, to the attitude of mind in which he approaches his problems. I think that there can, in any event, be no doubt at all concerning the magnitude of the change, not merely in detailed knowledge but in essential character, between the medicine of today and that of the older physicians. Long after the days of Laennec, surviving here and there, indeed, even into the present century, there was a prevalent attitude which regarded clinical medicine as an empirical craft, a scholarly tradition, and therefore as differing essentially from the experimental sciences in its aims, in its methods and in the criteria of validity properly applicable to the assessment of its evidence. Under such conditions, the researches of the laboratories could, of course, offer means of identification or measurement which, from time to time, would be recognized as aids to the clinician in diagnosis or treatment; but they would be technical contributions, and not a part of the same body of knowledge. And the contrast between the medicine of today and that which prevailed in 1868, and indeed for many years later, seems to me to have involved something much deeper and more fundamental than the progressive adoption by the clinics, even though its frequency increased in proportion to the rapid expansion of activity in the experimental sciences, of such technical aids to the discharge of an essentially different function. It has involved, I believe, a growing recognition that the work of the clinic, if it is to be effective under modern conditions and to make adequate use of the resources which are now becoming available from the laboratories, must accept the aims and the criteria of the experimental sciences—must itself,

indeed, acquire to an increasing extent the character of an experimental discipline, actively cooperating with an ever widening range of those which deal directly with other than clinical fields of knowledge and experience.

The fact of this change has, I believe, been generally accepted, but I do not think that there has been a corresponding unanimity in welcoming it as desirable. There must, I suspect, be some who still bemoan the loss of the special skill which enabled the old physicians, with no means of investigation but their finely trained and largely unaided powers of observation, to base their conclusions, whether of diagnosis or prognosis, and also their prescriptions of treatment, mainly on a rich store of experience, of which the contents were often beyond the reach of any attempt at detailed or conscious analysis. It was only natural, indeed, that the fullest development of this clinical instinct should be favoured by conditions in which very little else was available, and in which the concentration of the almost unaided faculties of inspection and physical examination, upon the whole patient, would not be disturbed by a consideration of exact data obtained by more elaborate methods, and each of them relevant only to some separate feature of his condition. Let the danger be admitted, that something might be lost of this special artistry of the clinician, when the impressions upon which it depended came to be supplemented or replaced by precise but partial methods of detection and measurement, as the science of the laboratories was able to offer these.

This danger should not be ignored; on the other hand, it should not be exaggerated. It is no part of the scientific method, or of the practice of the responsible scientist, to base upon scientific data, however precise and quantitative, conclusions which go beyond the limited range of their exact significance. So that, if any tendency was to be observed to make such a misuse of scientific data in clinical practice, it was not, I suggest, to be attributed to a detrimental intrusion of the scientific method, but, on the contrary, to the slow reluctance of some clinicians to acquire the scientific habit of mind, and to adapt their methods of interpretation to the inevitable change in the nature of clinical evidence. Clinical evidence was beginning to become an experimental science—a transformation still in progress; and although there might be reason to deprecate a hasty rejection of the old bottles of clinical empiricism, they would need to be progressively conditioned to hold an increasing proportion of the new wine of experimental science. Whatever view we may take of the gain and the loss entailed by this change in the character of medicine—I myself have no doubt that the gain, on balance, is great already, and that it will continue to grow—we are bound, I think, to accept it as a natural and inevitable development; and we may, with advantage, turn our attention to a rapid survey of some of the principal factors which have contributed to it.

THE INFLUENCE OF PHYSIOLOGY

In agreement with Dr. Singer, already quoted, I should regard the new

development of the experimental science of physiology, which had begun in the first half of the 19th century, with biochemistry budding from it towards that century's close, as having made, eventually, the contribution of widest and deepest significance to the change which we are considering. This influence of physiology, however, was of slow growth; and it was slower in this country than on the continent of Europe. For it was not until some years after 1868 that physiology began to get a firm footing in British Universities as a separate experimental discipline; and not until well into the present century that its influence on clinical medicine began really to be felt. Today it may seem so obvious as to be hardly worth mention, that medical conceptions of different bodily functions, normal or morbid, are intimately connected with the work of Sherrington and Adrian on the central nervous system, of Haldane and Barcroft on the respiration and the blood, of Gaskell, Langley and their pupils on the involuntary or autonomic nerves, of Bayliss and Starling on the contractile and propulsive functions of the abdominal viscera. It will be seen that I have chosen for mention only researches by British physiologists, and only certain outstanding examples of these. In any case, they are mainly products of the present century, and there was but little in 1868 to give promise of what was to come.

Still less was it possible then to foresee the development, which was not to begin in earnest until more than a quarter of a century later, of all our present wealth of knowledge concerning the hormones, or the vitamins, with its wide and deep influence on so many aspects of medicine. A good case could be made, indeed, for the origin of endocrinology as early as 1855, with Thomas Addison's publication of his remarkably concise as well as accurate description of the disease which now bears his name. It was not until 1891, however, that knowledge in this field made its first effective contact with practical medicine, when Horsley's experiments prompted Murray to treat myxœdema with thyroid gland substance. Thereafter came another long hiatus, until an even more striking outcome of research in this field, in Banting and Best's discovery of insulin, launched endocrinology upon its present career of astonishing progress. And it is to be noted that the multiple functions of the organ which was the subject of Addison's pioneer observations, the suprarenal cortex, are only now beginning to be revealed in all their complexity, by researches in which physiology, biochemistry, synthetic organic chemistry and experimental medicine are intimately cooperating. In the case of the vitamins, the delay was even longer. The cure or prevention of scurvy by fresh fruits and vegetables had been discovered, forgotten and rediscovered for several centuries; whilst the value of cod-liver oil in rickets had been on record since the 1840's and had even received practical application in the prevention of rickets in wild carnivores in captivity. It was not until 1919, however, when biochemistry had sufficiently advanced to make nutritional needs a matter of exact and systematic investigation, that the lack of a vitamin as the cause of rickets was experimentally proved; with the result that rickets as a practical

problem disappeared in a few years. It seems clear, then, that the due influence of physiology and biochemistry on clinical thought and practice has only quite recently begun to be felt; and I think that we need not hesitate to predict that this influence will yet become stronger or that, with the progressive permeation of clinical ideas and activities by the spirit of research, the influence will become increasingly reciprocal.

BACTERIOLOGY AND IMMUNOLOGY

One of the most revolutionary of all the impacts of experimental science on medical thought and action came, however, much earlier, and from a different direction. The appointment of Louis Pasteur to the Chair of Chemistry at Lille in 1854, and the contacts which he made thereby with the fermentation industries of that city, had opened the way to the series of researches, extending over twenty years, which demonstrated that self-propagating living organisms are responsible for fermentative and putrefactive processes of all kinds, and established the validity of the principle of biogenesis, under all conditions which have, so far, been open to investigation. The first application of this new knowledge to problems of human medicine came, however, not from Pasteur or any of his immediate associates, but from our own Joseph Lister, whose evidence that suppuration and septic conditions generally were due to such bacterial infections, began to be published as early as 1865. It is noteworthy, however, that neither Pasteur's evidence for biogenesis, nor Lister's antiseptic surgery, had fully established themselves by 1868, against the resistance of a large body of scientific and surgical authority in their respective countries. The award of the Copley Medal of our own Royal Society to Pasteur, in 1869, appears to have been regarded in some quarters as a somewhat bold endorsement of a heresy. The application of the new bacteriology to problems of infectious diseases in general, in man and animals, began only towards the end of the 1870's, and then rapidly extended in the following decades. Soon followed an associated experimental study of immunity, on the artificial production of which some of the pioneer demonstrations had also been given by Pasteur himself. And thus bacteriology and its extensions, including the study of pathogenic protozoa from the 1880's and of the invisible viruses from the 1890's onwards, has transformed the whole attitude of medicine to the infectious diseases, and all the methods of recognizing and dealing with them, whether by preventive or curative treatment, and whether in the individual patient or, by public administrative application of the new knowledge, in whole populations. As a later development, the preventive and curative applications of immunology have been most powerfully supplemented by chemotherapy, for which the initiative and inspiration came from Paul Ehrlich. And there is, indeed, no more striking contrast to be found between the medicine of 1868 and that of the present day, than that between the helpless, expectant attitude to the treatment of infectious diseases in 1868, and the well-grounded confidence of today in the direct

efficacy of the wide range of immunological, chemotherapeutic and antibiotic remedies already available, and still rapidly extending.

RADIOLOGY AND OTHER SCIENCES

The *discovery of X-rays* in 1895, and of *natural radioactivity* in the following year, opened a great new, and still rapidly progressive, chapter in 'physics', which until then had appeared to be almost a closed book, subject only to completion or emendation in detail. And it is to be noted that the beginning of a new and cooperative relation, between medicine and the experimental sciences, was signalized by the rapid and eager application of these resources of the new physics to medical uses, in diagnosis first, and then in treatment. The process continues in full vigour, so that medical radiology is now in the forefront of enterprise, in finding medical applications for the newest sources of ionizing radiations, which the present forced development of nuclear physics is making available in such wealth and variety.

Modern *genetics*, again, provides an example of an even more recent development in the experimental sciences, of which the significance in relation to medical problems, though its exploration has so far been but partial and tentative, seems certain to provide the basis, eventually, of a new and most important cooperative enterprise for medicine and biology.

Many other examples could be cited; but the general direction of the change, and the certainty of its further progress, will hardly, I think, be in doubt. If space were available, something could also be said of the change, quite obscure in its causation, in the nature of the problems presented by some diseases, as well as in the spirit and the method of medicine's approach to them. The decline in the severity and potential danger of scarlatina, easily to be observed within living memory, is a noteworthy example; from the standpoint of today's experience one has a vivid sense of contrast, in finding that a great clinical observer of the old school, Samuel Wilks, writing in 1863, described scarlatina as then 'the worst form of specific disease existing in this country'.

Probably the most dramatically obvious of all the contrasts, however, between medicine in 1868 and at the present day, is provided by a comparison between the resources available and used for medicinal treatment, then and now. It is a contrast between the empirical administration, then, of traditional remedies largely of no clearly recognizable activity and, in any event, with no expected result beyond the alleviation of certain symptoms; and, on the other hand, the present-day use, with confidence and precision, of remedies with clearly defined and measurable actions, many of them concerned with the direct removal of the causes of disease, and not merely with the assuagement of its symptoms.

THE SOCIAL BACKGROUND OF MEDICINE

By SIR HENRY BASHFORD, M.D., F.R.C.P.

FROM a technical point of view, the span of years covered by *The Practitioner's* life embraces a period of advance in Medicine and Surgery for which there had previously been no parallel. Although anæsthesia, as a routine accompaniment to surgery, was some twenty years old when *The Practitioner* was born, bacteriology as a practical science was scarcely above the horizon. It is true that, in the previous year, Lister had announced the first results of his Glasgow experiments in antisepsis, and Clifford Allbutt had just introduced the pocket clinical thermometer. But the ophthalmoscope, auriscope, and laryngoscope, as daily means of diagnosis, were still awaiting the future, with radiology, insulin, antibiotics, and the major part of chemotherapy. The General Medical Council was ten years old, but the Medical Register and the British Pharmacopœia were not yet in their teens. Nor was the Nightingale Home at St. Thomas's Hospital, which was to set a new standard for nursing. Apart from gynæcology and obstetrics, there were few specialties, and although some physicians and surgeons tended to be more interested and consulted in particular branches of their cult, they were all predominantly general practitioners.

Blood-letting as a panacea had nearly died out. But blood transfusion was more than half a century distant. Sufferers from pulmonary tuberculosis, or most of them, passed their days behind carefully shut doors and windows. Scores of young women, if they were not land-workers or dairy-maids, were green with a chlorotic anæmia that few medical students of today have ever seen. In the wealthier groups of the community, numbers of people were permanently lying upon sofas or doomed to lives of inactivity owing to innocuous murmurs of the heart, whilst their poorer counterparts—driven by economic necessity—were proving how right, a couple of generations later, James Mackenzie was going to be. Inflamed appendices, undiagnosed, were culminating in general peritonitis and death and if, by some alchemy, a medical student of 1951 had been able, with the eye of a Cobbett, to make a series of rural rides during *The Practitioner's* infancy, few could now blame him if he had returned shocked by the relative ignorance that he had met.

THE MID-VICTORIAN ERA

But he would probably have found, if he had confined his studies to the profession itself—its general composition and the sort of men in it—that the subsequent changes had been less and much more superficial than those in their knowledge and technique. Like the priesthood with which, in medieval times, it had been so closely identified, he would have found it very catholic in its recruitment; and he would almost certainly have dis-

covered in it a strong hereditary element. In 1902, Sir Arthur Keith, studying a group of 100 medical students and doctors at the London Hospital, showed that nearly a third of them were themselves the sons of doctors. In 1951, an analysis of the 848 Fellows of the Royal College of Physicians elected between 1825 and 1925—excluding those still alive—showed that, of the 422 whose fathers' occupations were known, 164 had been the sons of doctors. Another large contingent had been sons of the rectory or the manse, and many others—the majority of the whole—sons of professional men. But there was a substantial contingent whose fathers had been in business, large or small, and the rest included sons of farmers, craftsmen, and a little group who had been the sons of larger landowners and country squires.

It was certainly the case that, by mid-Victorian standards, the profession was not regarded as in itself conferring 'gentility' in the same sense as ordination into the Church of England or a regular commission in the army or navy. In fact, George Eliot, writing in 'Middlemarch' of some thirty years before, describes her Lydgate—of whom Clifford Allbutt is believed to have been the original—as an exception among country doctors in that he was the son of an army officer, had been to a public school, and was acceptedly a 'gentleman'. And Lady Chettam's remarks, before she had met him, may be remembered: 'One does not expect it in a practitioner of that kind. For my own part I like a medical man more on a footing with the servants'. But if, as an old lady, brought up in Mayfair, observed to me in my youth, doctors were not the sort of people who were usually called upon in her own young days, there were at least some who were. Hadn't

1869

WISE IN HIS GENERATION

Fashionable Patient: 'COD-LIVER OIL!!! MY *DEAR* DOCTOR. I COULDN'T TAKE SUCH HORRIBLE STUFF AS THAT!'
Fashionable Doctor: 'WELL—WELL—WHAT DO YOU SAY TO—A—CREAM AND CURAÇAO?'

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one of the Herberts become a doctor and served as such during the Franco-Prussian War? And nobody could deny that the medical was a noble profession.

Indeed, this particular view of it—with what some would regard as typical Victorian sentimentality—seems to have been taken much more generally than has since become the fashion; and the great novelists of the period were very kind, as a rule, to their doctor characters. Thus, Charles Kingsley's Edward Thurnall, in 'Two Years Ago', was 'beloved and trusted by sick and poor' and no 'purer or gentler soul' had ever entered a sick room; and if his son, Tom, the hero of the book, was slightly improbable as a Fellow of the Royal College of Surgeons, he was the beau-ideal of a man of action and, by the end of the book, had avowedly become the type of muscular Christian which he always was in essence. Trollope's Dr. Thorne—who 'loved to consort with low company', though himself the cadet of a land-owning family—is one of the most endearing of all his characters; and Luke Fildes' celebrated picture 'The Doctor', although it may since have been gently smiled at, deeply stirred a responsive chord in many thousands of his compatriots. Just as within the profession itself there was a vocational brotherhood ignoring differences of birth and upbringing so, from outside, there was in fact a tendency to look upon it as something *sui generis* in the national economy, with its own code and passports.

In spite of the Lady Chettams, the ordinary country squire, however caste-conscious, would have thought it much more natural to see the local

1865

EARNING THE CERTIFICATE

Family Doctor: 'AND NO PORT, MIND; IF YOU DRINK PORT WINE YOU'LL HAVE ANOTHER ATTACK OF GOUT, AS SURE AS FATE.'
Country Gentleman: 'QUITE CERTAIN?'
Doctor: 'NO DOUBT ABOUT IT.'
Country Gentleman: 'THE VERY THING. YOU STAY AND DINE; WE'LL HAVE SOME OF THAT "THIRTY-FOUR," AND—I'M SUMMONED ON A *JURY* THE DAY AFTER TO-MORROW!'

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doctor sitting over the port with him after dinner than the neighbouring mill-owner, however wealthy. If an occasional baronet's son, too, became a doctor, there were more doctors who became baronets, and even Victorian snobbery—probably in retrospect now exaggerated—did not regard this as at all inappropriate. The great Queen's own first medical adviser and close friend—responsible for the creation of Balmoral—was the son of a Scottish farmer, and one of his successors, whom she insisted on seeing every day and who married one of her ladies-in-waiting, was the son of a village doctor. James Young Simpson, her physician in Scotland, had come from a small baker's shop. The famous Sir William Gull was the son of an Essex barge-owner, and Sir Thomas Spencer Wells the son of a St. Albans builder.

THE CHANGING FACE OF MEDICINE

But the average doctor, then as now, had probably not been led to adopt his profession for social reasons and, then as now, was probably not greatly concerned about degrees of merely social status. He was, no doubt, extremely jealous of the honour and integrity of his own profession—a jealousy that the public shared and had approved, if largely for its own protection, in the shape of the new General Medical Council and the Medical Register. But his own work, whether scientific or clinical or both, was far too engrossing to leave him much time for anything else, though possibly rather more than increased academic and administrative requirements have left to his successors. And it is at this point, perhaps, that our medical Cobbett might have begun to notice some differences. He would have found that a greater proportion of doctors, especially among the consultants, had supplemented their studies at home with visits to continental seats of learning. He would almost certainly have found more of them familiar with the classics, contemporary literature and art than was the case with his own generation. If they were less well equipped as doctors, they were more widely educated as men. He would also have observed—at any rate in the larger towns and cities—a greater formality in personal attire, in the almost universal top hat and frock coat that were to take so long in disappearing. He might have been amused, too, by the Victorian delicacy in respect of fees—again especially among the consultants—the unobtrusive pushing by the instructed patient of a guinea or two guineas behind a book or an ink-pot, doubtless observed by the consultant but without any undignified hint that he had done so. He might even have beheld, as at Sir James Young Simpson's, a bowl on a waiting-room table into which the patient's honour was trusted to place a suitable emolument. Odd phrases, too, would have struck him—surgeons solemnly discussing whether some particular kind of pus could justly be described as 'laudable', and physicians advising that such or such a drug should be 'exhibited'.

Out in the country, of course, it would have been otherwise. The gaitered village doctor on his sturdy horse would have seemed, in his more careless and comfortable garb, much more akin, in this particular detail, to his

successors of today. But among these country and small town practitioners, he might have found, if they could have bridged the years with him—could still, indeed, find among some of their older living descendants—a certain regret for changes of which they, more than he, would be aware. These present-day young men dashing about in their motor cars, with their hypodermic syringes, their blood-pressure apparatus, their penicillin and books of certificates, were no doubt abler technicians, making much more correct diagnoses and saving their patients from disasters that they themselves could not have prevented. But they did not seem to be on quite the same intimate terms with them. They were not being asked, for instance, by Mrs. Smith at the grocer's shop to tell her why her accounts wouldn't come right, to help old Mr. Robinson with his will, or to advise Mrs. Jones upon a suitable career for her youngest son. They were no doubt just as respected. But they were now being called in—and seemed to take that for granted—more as if they were skilled architects or engineers and less as if they were founts of general wisdom, more as mere experts and less as family friends. It was nobody's fault, of course. Perhaps it wasn't a fault at all. These young men were busier—had to be busier—keeping themselves up to date in the ever-growing and complex ramifications of their craft; and perhaps it wasn't so easy to pull up a motor car as it had been to lean down from a horse and chat with a shepherd under a hedge, listening to and sharing his domestic problems.

1874

'IN MEDIO TUTISSIMUS'

Country Practitioner (about to go up to London on business): 'I SHAN'T BE MORE THAN TEN DAYS AT THE FURTHEST, MR. FAWCEPS. YOU'LL VISIT THE PATIENTS REGULARLY, AND TAKE CARE THAT NONE OF THEM SLIP THROUGH YOUR FINGERS—OR GET WELL—DURING MY ABSENCE!!'

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On the other hand, in the industrial towns and their back-street practices, in the dock-yard areas of Liverpool and Glasgow, in the East End of

London, those relationships had never, in the same sort of way, existed; and few would have been found to shed a tear over the changes there. Competent men were, without doubt, doing good work in these areas from the beginning —when Blake's 'satanic mills' had started spawning them in such quantities —and were certainly to be found there fifty years ago. But most of those who had been able, out of their shilling and sixpenny fees, to save money early enough and quickly enough had been wont to depart for more salubrious neighbourhoods; and for those less fortunate it had been all too easy —in the absence of local culture and criticism—to rely more and more, as they grew older, on fatalism and bluff. These were the places, too, in which the less competent had tended to find a refuge. Even so, the aura of their profession had surrounded them, and they had been able, single-handed, to visit secret corners and alleys where the police would only venture in two's and three's. There had also been a foreshadowing of things to come in the private twopence-a-week clubs that some doctors had established there for the benefit of their poorest clients—treatment the same but no paper and sealing-wax on the bottles of medicine. Grim, however, as these areas still remain, the worst of the older slums have gone. The schools and the sanitarians, the stricter licensing laws, the arrival of the cinema, the routine bottling of milk by enlightened distributors, and the panel system—following the much criticized National Health Insurance Act of 1911—have all contributed to improve conditions both for patients and doctors. With fewer bad debts and less work compelled, for humanity's sake, to be done for nothing, medical practice in these districts has

1893

THE NEW DOCTOR

'THE *HIDEA* OF A YOUNG MAN LIKE THAT A-TELLING O' *ME* 'OW POOR PEOPLES' CHILDREN HOUGHTER BE FED AND LOOKED AFTER! WHY, I'VE BURIED FOURTEEN O' MY *OWN!*'

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become a much more financially secure and, in many more important ways, a particularly rewarding sphere.

THE PRESENT-DAY OUTLOOK

Further changes have, of course, taken place influencing every kind and mode of medical practice. The country doctor on his horse, still to be met in the early 1900's, his urban counterpart hopping in and out of his neat and familiar brougham, the provincial and metropolitan consultants with their carriages and pairs, their white waistcoats and gold watch-chains, their elaborate and hospitable dinner-parties—all these have gone with something that has not been replaced in the era of the telephone and internal combustion engine. The great fortunes left by the leading, or most popular, surgeons and physicians from the reign of Queen Anne to that of George V seem unlikely ever to be accumulated by their followers of today or in any probable future. More and more the community has taken the view that the health of each of its members affects, directly or indirectly, the vitality and efficiency of the nation as a whole; that all should share in making available to each the full resources of Medicine and its ablest practitioners; and that what was once left to philanthropy should be undertaken as a national obligation. And all this has meant that the doctor has increasingly become the servant of the community, paid by the community on agreed terms, and less by the individual.

Developing from its earlier expression, during the last century, in the establishment of an order of doctors solely concerned with such problems as the control of infectious diseases, urban and domestic sanitation, and the hygienic preparation of foodstuffs, this view has since widened to embrace both industry and the home to an extent that the Victorians—if they could have foreseen it—might have regarded with some misgivings. It has, of course, made the profession much more influential in many ways. Far more than ever before, doctors have become the routine colleagues of statesmen and those responsible for industrial production. But in so far as all politics are, at any one time, a compromise, has this not endangered, the Victorian doctors might have asked their successors, professional and personal independence? Whilst there was much to be said, too, for making it easier—though it was always possible—for a boy, however poor his parents, to enter the medical ranks and for the younger qualified men to become consultants, if they so desire, what about the price to be paid? Would it not mean, they might also have asked, a sacrifice—possibly an atrophy—of valuable qualities, the sort of qualities that made a Gull or a Simpson or a Farr?

Time alone can reveal the answers. But all these developments, together with more recent changes in the machinery of general practice, hospital management, and methods of payment, are changes, after all, merely of externals. They do not affect the motives, scientific or humanitarian, which have always attracted men to Medicine. Nor can they touch what, in the last analysis, are its deepest demands and rewards.

TRENDS OF GENERAL PRACTICE

A HUNDRED YEARS IN A YORKSHIRE DALE

By WILLIAM N. PICKLES, M.D., D.Sc., M.R.C.P.
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AND yet he was not so old, he reflected, but no one lived to be old in this practice. There was Matthew Willis who preceded him, tall and gaunt with intelligent black eyes and profuse mutton-chop whiskers. He, poor fellow, had a large hæmoptysis—ruptured a blood vessel as the villagers said—while out riding that gingery mare of his. He just managed to win home, but that was the end. He never afterwards left his bed. And how he was beloved. An appeal went out for a suitable memorial to him and the whole required amount was subscribed in a few days. There the memorial was in the Parish Church, a hideous stained glass window of Christ healing the sick. He wondered whether there would be a memorial to him in due time, for he knew he lay a-dying. He knew it by his breathlessness and those thick dropsical legs, which were as heavy as lead. No remedy had helped in the slightest degree. Even his favourite Succus Taraxaci and Mag. Sulph. mixture had done nothing but make him feel slightly sick, and those uncomfortable Southey's tubes gave only temporary relief. He even tried, surreptitiously, the local dropsy cure, *'pellitory of the wall'*—wouldn't that lanky young assistant of his have laughed, had he known?—but he felt he grew gradually worse, and he was only fifty-six. He had had a hard if satisfying life and that nasty trap accident three years ago had not helped matters. But his mind wandered back to those other doctors. Some of them had not been too temperate, and his blue lips parted in a smile when he thought of one languishing in the stocks, traditionally their last occupant. Ah, he'd taken that village feast far too seriously! He thought of that bottle of gin demanded at each arrival into this world, and this reckless fellow, helped no doubt by the kind-hearted gamp, leaving no single drop. But he had many adherents and these used to say that he was a better doctor drunk than many a one sober. No one could be kinder in their troubles and no one more considerate to the poor—and there were poor in those days—and so easy in his charges.

THE OLD PRACTITIONER PASSES

Now his housekeeper interrupted these thoughts, 'Would he see the Vicar?' 'No thank you', said Baker with a return of his gaiety and ready wit, 'Tell him I always deal direct with the head of the firm', and as she glided from the room to soften this somewhat blunt refusal as only she knew how, aided no doubt by a glass of the doctor's golden sherry, his mind again wandered back to the past. He felt he had lived at a difficult time in medicine. He had

been taught good sound stuff at Mary's. He could set a broken limb with anybody and no one in his hospital days thought much of that Quaker fellow in Glasgow with his fantastic ideas and his claim to have healed compound fractures by first intention with the help of that foul-smelling stuff of his. Now, a German had invented a machine by which you could

FIG. 1.—The stocks referred to are those in West Burton. They are seen in this view of the village in front of a monument erected to commemorate the Battle of Waterloo. The structure is said to have replaced one of the 'butter' crosses at which farmers' wives held an unofficial market in many of our villages to find purchasers for their butter, eggs, curds and cheese.

actually look through the flesh and see the bones. In a way he felt he had not needed it. He had relied on the touch of his sensitive fingers and a keen eye for alignment; and then he took infinite trouble. One had to live with one's failures as well as one's successes in a country district and, ah, yes, there had been one at least of the former. The postman who limped about his rounds was a living reproach to him, but that was only one failure among so many successes, and he wondered whether those who followed after, even with the help of these Rœntgen rays, would have a better record. He thought of the succession of young assistants and how he used to defer to their more recent experience. The patients used to tell them: 'Dr. Baker thinks ye know more than he does, but we don't'. Of course, they were all ardent Listerians, and after all Lister was now a Lord so there must have been something in what he said. These lads boiled their instruments, and

stitches and scalp wounds and those nasty gashes in arm and leg from the hay field healed in no time and without the intervention of laudable pus which had so often been the fate of his efforts; but they still called him in for his advice and his clever manipulations in midwifery cases and he knew he could handle those forceps even now and deliver a poor woman when others failed.

Now these young fellows had their bicycles. Handy they were, he didn't deny, but oh, what a loss of dignity. He thought of himself with some satisfaction, proud of his horseflesh. How he did love his horses—Betty, the best of the lot. His friends wanted him to call her Stella from that star on her black forehead, but Betty it was, and no one knew the reason or that other reason closely connected with it, why he had never married. He thought of the shiny top boots, tan breeches and black coat. He thought of bowling along in his smart gig, when it was too hot to ride, or in winter gliding over the snow with all the glamour of sleigh and bells, himself in that warm fur coat old Dives had pressed upon him when he pulled his son through double pneumonia.

FIG. 2.—Baker with his man Lambert in the gig with Betty in shafts, crossing the ford over the River Ure near Aysgarth. The 'Strands' are seen to the right of the picture.

The very idea, these young fellows nowadays stipulated for holidays! He never had a holiday except a few days in Liverpool to visit his sister and give her advice in her widowhood. To be quite honest he generally contrived these visits should include a certain Friday in March, when he would

have a great day at the Grand National and carry back memories of it for the rest of the year. But he had his recreations at home. He could always spend a few hours down by the stream and go home with a good basket of trout, and those days on the moors after driven grouse, weren't they good? In his heart he still preferred to walk up the birds alone with his dog and his greatest joy of all was in that marshy land, the 'Strands', by the river where he could almost always fell a 'jack' or a 'full' snipe, and he fancied himself at snipe and woodcock.

FIG. 3.—Alfred Baker's kindly, humorous face was always welcome in the sick room. He was five foot four in his socks and rather plump. His friends likened him to Pickwick, which character indeed he impersonated at some *tableaux vivants* in Aysgarth. He began practice in 1873, and died early in 1903.

This young fellow who seemed likely to succeed him was tip-top, a regular thruster with good theory and practice. Why, he actually had a surgeon over from Leeds, a likeable youngster with thinning reddish hair and keen clear eyes, some weeks ago. He came on the last train to see a lad with inflammation of the bowels, and with only a paraffin lamp for light and the kitchen table to operate on, these two had removed his vermiform appendix and the lad was now back at work. How he had dreaded those inflammations of the bowel. So many of them recovered in time with linseed poultices and a dose of castor oil, but some slipped through his fingers, and now this young fellow said they should be operated on. Of course, he knew this. When he came into practice first he was an assiduous reader of his journals. He had tried to keep up-to-date and he had read at intervals of this procedure, but the application had not been easy.

His long after-dinner talks with this assistant over the modest two glasses of '68 had shown him how he had lost touch. They were actually opening the bladder above the pubis for removal of stone and that age-old spectacular lateral lithotomy was a thing of the past. This young fellow announced his intention of spending part of his cherished holiday at his old hospital—'Getting a rather better insight into cutting', as an old man in the village expressed it, and Baker only wished he had done so in his thirty years of practice.

THE NEW MAN TAKES OVER

Here we leave Alfred Baker, this cheerful manly little fellow. There are two memorials to him, one alongside that stained-glass window in the Parish Church and one in the village Institute, that Institute for which he fought and which he obtained against great opposition and to which he contributed fifty pounds, which was about all he had in the world. He died almost with the beginning of the century and his energetic and mobile young successor doubled the size of the practice, for did he not with judicious use of bicycle and train cover far more ground than even little scampering Betty, one of whose hooves, alas, mounted in silver now appeared on his writing table as an inkstand, but was he not soon the possessor of that fine Darracq car.

Such a thing had never been seen in the Dale before. Full of fun and still having much of the boy in him he used to terrify those who rashly accepted a lift as a new experience by travelling, I suppose, at about twenty-five miles an hour, or as fast as the contraption would go. 'Willie' was a different proposition and his answer to Hime's inquiry as to whether he were frightened was 'It's thy bloody neck as well as mine, doctor'. But even this fine car was not altogether reliable and many a time did the able-bodied turn out good-humouredly to help push an inert wheeled object up the hill into the village; 'Jammie Hill' as it is still called after Jammie Thompson the shoemaker who lived at the top of it.

Hime had imbibed much from little Baker in their few years together and was a sound obstetrician according to his lights. He was a useful surgeon, knowing his limitations, and he appears to have been a fine physician. He was determined to be more than a simple village apothecary, as he told a retired Indian Civil servant staying at the Palmer Flatt Hotel who announced pompously that he paid his town doctor ten shillings a visit, but only expected to pay five in the country.

His training had been different to Baker's, and the latter looked upon his flair for the diagnosis of those acute abdominal conditions as almost miraculous and his decisions as to when to send for that young surgeon friend of his were nearly always right. To his everlasting credit that young friend always came, although as a rule his hope of adequate payment was slight. He knew when he was sent for to Aysgarth his presence was necessary and that his would be a life-saving journey.

In his midwifery practice he found he was at first up against tradition. He insisted so on cleanliness, the prevailing practice of retaining the used nightdress or even day clothes, being styled a gipsy habit. 'Can't you give her something to help her' the old handywoman would say, but he had been taught not to give ergot before the birth of the child, as Baker invariably did, and he had to risk being thought difficult. The night bell was often the first intimation that a birth was expected. Even the specialist attending the wealthy would, of course, like to make the lady's acquaintance before the

event, but seldom thought it necessary to do more. When Hime was told beforehand and made a note in his little book the dates were not always correct. The handywoman on his good-natured protest would say 'Ay, she's a bad counter', or, 'She's laid her cinders wrong', referring to the custom in illiterate days of placing a cinder on the mantelpiece for each missed period so that when it came to the tenth the birth was known to be imminent.

These helpers were at times the bane of his existence. They would either send for him ridiculously early or, what he minded more, far too late. They were self-opinionated and would exasperate him by quoting long obsolete practices of his predecessors, but he never quarrelled with them for he knew in his heart what fine unselfish creatures most of them were, giving their help and hours of sleep voluntarily and scorning to take pay for their services. Any country doctor could say much of these motherly women and how with tact and firmness their usefulness could be increased. The personal touch was there, and they had woven themselves into the fabric of village life and carried on year after year, often being a source of comfort for at least two generations. 'We'll have Maggie', prospective grandmothers would say to their daughters, 'she were with me when you were born'. There was continuity in their services which can never be attained by their successors, however much these may transcend them in other ways, and they were mines of information. If one followed the Yorkshire adage 'Hear all and say nowt' one would hear many useful pieces of information about one's patients, and I, personally, here and now acknowledge my indebtedness to these sources in various investigations.

Hime found the bottle of medicine dear to the patients' hearts, and if there is one thing that has remained stationary it is the faith in that bottle. We ourselves should be much handicapped without the psychological effect of these bottles, and after all they are reasonably cheap, whereas complete X-ray examinations and physiotherapy often acting in the same way are very expensive. No one, lay or medical, had the slightest idea before the National Health Service made its appearance three years ago how much self-medication there was in the land and how much physic daily went down His Majesty's subjects' throats. In the early days of the century there was one preparation amid the hosts of palliatives and placebos which really did appear to work miracles, and had not this doctor found this so in his treatment of that lad whom he had no difficulty in diagnosing as a cretin, and in the same village, where also most of the girls had disfiguring goitres, of that middle-aged woman whom he rightly regarded as myxœdematous?

THE THIRD GENERATION

Such was the practice my partner and I succeeded to from Edward Hime in 1913, and further progress was slow. Horses were still used and cars were improving but were not quite reliable, and their constant use was not financially consistent with the income from the practice. The motor bicycle

was a distinct advance, but the early ones stood high above the ground and many a 'toss' we both took riding these in our hilly difficult district. In Baker's early days he was the only possessor of a paraffin lamp in the village and even candles were used sparingly in a thrifty population of minute incomes. Knitting for its own use or for sale was a village industry, and the old inhabitants used to tell how to save light and fuel they would congregate in each other's houses in turn, and even then when knitting was in full swing the candle was extinguished as no longer necessary. Now, thanks to local enterprise, we were to have electric light, harnessing our swift running mill race for the purpose.

Gradually amenities grew. The small car was found to be the solution of our transport difficulties, but what gave us a pang was that the horses, no longer essential, had to go. Expenses were high and although our income was considerably increased, and with ready money also, by the N.H.I., it was no longer justifiable to employ regular labour, and that picturesque figure, the doctor's man, disappeared from our practice as from so many others. Earlier in that period messages by day came in the exasperating and monotonous formula 'Come at once' by telegram. By night the horse had to be saddled or harnessed or the bicycle fetched out, the trouble it gave the patient's relatives being at least a sign of sincerity. Baker's speaking tube is still in existence by means of which he could commune with the messenger without leaving his warm bed or letting in the unwholesome night air. In the end the telephone, at first a source of irritation and a negation of all privacy, was accepted as a necessity.

Later, it was found possible to get the sufferers from acute surgical conditions to hospital, first in the closed car and then by ambulance; a few even by rail on a stretcher in the guard's van in the early days. This naturally took away much of our interest but was definitely in the patient's favour. Apart from the forensic aspect, it was realized that all fractures must be X-rayed, and, with transport facilities improved and apparatus available at a reasonable distance, this was effected.

The marvels of insulin brought us fresh hope and many a young life was snatched away from an early grave. It is not proposed to review in detail the romantic period of wonder drugs, beginning not so very long ago with the early sulphonamides. This epic is well known to most readers as a personal experience and for the younger the information is readily available elsewhere. Suffice it to say that taking only acute lobar pneumonia as an instance, its terrors have departed. In the old days, a sufferer from this disease monopolized our attention for all that period preceding the longed-for crisis. It was unusual for us to attend such sufferers without the help of a resident nurse, and to say that now we never think of such an extravagance, even if these ladies were available, shows how the outlook has changed. District nurses, each with her car, have helped us enormously in treating our sufferers from acute medical conditions and in so many other ways, but many of us

long for the small home where we could admit these patients and do so very much more for them.

In a recent visit to Australia and New Zealand, I have been struck by the relatively small amount of visiting undertaken even in country districts. A provisional diagnosis appears to be made by 'phone, and if the patient is thought to be seriously ill, he is brought by ambulance or car to hospital and detained, should the bill prove a true one. Domiciliary midwifery is almost unknown. It cannot be said that these practices should be adopted in our country, even if the beds could be made available, but they do make for an enormous saving in medical man power, and there is no loss of personal touch as the patient still retains his or her own doctor.

Midwifery in our own country districts has been revolutionized although it is still in the main conducted in the patients' homes. Aided by the district nurse-midwife, there is now an adequate antenatal and postnatal service, and the fees received under the N.H.S. are a distinct advance on those we were wont to ask our patients to pay.

EPILOGUE

In Australia it was rare to leave any assembly without being asked to express an opinion on our National Health Service, and I feel I must finish on that note. At the Editors' request I have written these pages about one practice—and that my own, confessing complete ignorance of any other, and I cannot express too strongly my feelings of delight and relief when I threw aside day book and ledger. The new conditions have been established almost imperceptibly and without disturbing the doctor-patient relationship which existed before. I recall the remark of a patient in a country practice to a visiting specialist 'Our doctor looks upon us all as members of his own big family'. That I believe was an accurate summing up of the position, and such a relationship is the precious possession of the general practitioner, which must not be sacrificed. With the cost of modern treatment it was becoming increasingly difficult to obtain adequate remuneration from our patients, and under the new conditions, although the incomes earned are still too small, they are some improvement on the old.

Little Baker and his like, whose patients' needs were their first concern in life, would have rejoiced could they have foreseen how much more was to be done for them with the changing times.

ADVANCES IN MEDICINE

By SIR HENRY COHEN, M.D., F.R.C.P.
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ALTHOUGH there have been important contributions to our knowledge of the mechanisms and control of disease in many fields, the dominant themes of therapy in the past year have continued to be the development of antibiotics and the uses, hazards, and limitations of the adrenocorticotrophic hormone (ACTH) and cortisone. Striking evidence has accumulated of the changes wrought in medical practice by chemotherapy, and this continues to overshadow all other advances. The volume of industrial production of antibiotics is tending to outrank all other medicaments. Penicillin and streptomycin account for at least half of the drug bill of many large hospitals. The treatment of infectious diseases has been so simplified that interest in them is beginning to flag, and students are restless with the irksome details of bacteriology when they learn that 'aureomycin will cure most bacterial infections'. Not tens but hundreds of antibiotics have been tested for their therapeutic potentialities, and for these, soil-organisms have been so fruitful a source that the words of Ecclesiasticus merit recall—'The Lord hath created medicines out of the earth, and he that is wise will not abhor them'.

Within the last two years the three antibiotics which have attracted and merited most attention are *chloramphenicol*, *aureomycin* and *terramycin*. *Tyrothricin* and *bacitracin* have been shown to have a limited use; *polymyxins* are toxic, especially to the kidney, although recent less toxic preparations appear to have a special range of usefulness in *H. influenzæ* meningitis.

The generous provision of facilities and funds by many large pharmaceutical manufacturers will certainly lead to the discovery of many more effective antibiotics—'That which they have done but earnest of the things that they will do'. But our justifiable jubilation at recent victories should not blind us to the conquests yet to be gained—the common cold, influenza (the toll of which was again exacted in a widespread epidemic earlier this year), and poliomyelitis. These still repel the chemotherapist's offensive.

THE SULPHONAMIDES

Present evidence suggests that sulphadiazine and sulphamerazine remain the most effective agents in meningococcal infections, Shigella dysentery, and certain urinary tract infections. In all other infections the appropriate antibiotic seems to be superior to the sulphonamides. These are, however, still widely used, for they are therapeutically effective, easy to administer, and inexpensive. But their toxic effects are troublesome, and the possibility has been suggested that they may play a part in the alleged increased incidence of collagen diseases. Therefore, unless there are clear indications

for their use, either in prophylaxis or treatment, they should be withheld, and here it is of importance to record that clinical impressions which had led to the use of sulphonamides in the treatment of acute tonsillitis and acute 'sore throats' receive no support from two controlled investigations during the year (Macdonald and Watson, 1951; Landsman *et al*, 1951).

PENICILLIN

There is an increasing preference for preparations which produce higher and more prolonged penicillin blood levels, and further evidence has been provided to show that procaine penicillin with aluminium stearate is more effective than procaine penicillin in oil or water, or penicillin in oil and wax (Cannon *et al.*, 1951).

Penicillin has found few more effective uses than in the treatment of acute bacterial pneumonias, yet in chronic respiratory infections, such as chronic bronchitis, bronchiectasis, and chronic lung abscess, even when these are associated with organisms of proved penicillin sensitivity, the benefit from systemic penicillin is but slight. The explanation may well lie in the increased permeability of the alveolar epithelium to blood penicillin in acute inflammatory states, for in these, upwards of 0.04 unit of penicillin per ml. can often be detected in the sputum, whilst in chronic infections when most of the disease is in the bronchi or in epithelialized cavities, there is an effective barrier from the blood stream. This has led in the past few years to an increasing use of penicillin and other antibiotics by inhalation as aerosols. Recently it has been claimed that the hydriodide of benzyl penicillin diethylaminoethyl ester (marketed as 'estopen') has an exceptional affinity for the lungs and is selectively excreted, so that relatively high penicillin concentrations are produced in the lungs and bronchial tree (Heathcote and Nassau, 1951).

Among penicillin's most spectacular conquests is ***subacute bacterial endocarditis***, which in earlier days had been an almost invariably fatal malady. Now 60 to 70 per cent. of its victims survive.

Cates and Christie (1951) have gathered the long-term results of treating 442 cases in various centres throughout the country from 1945 to 1948. They now advocate a larger dose of penicillin—two million units daily for four to six weeks, and even larger doses for the more resistant organisms. It is found that when relapses occur, they tend to appear early: in 75 per cent. within twenty days of the cessation of treatment, in 92 per cent. within a month. The risk of delayed relapse or reinfection after six months of apparent cure is only 2 per cent. per annum. Similar findings are reported by Gorlin (1950) from America.

The chief obstacles to successful treatment are heart failure (the most important factor in prognosis) and penicillin-resistant bacteria, especially enterococci. Several reports have appeared during the year describing benefit in resistant cases from larger doses of penicillin (20 million units daily) combined with streptomycin (4 grammes daily) for at least six weeks. The risks of vestibular damage from such large doses of streptomycin are high. The studies of Kane and Finn (1951) confirm that penicillin is still the

antibiotic of choice in subacute bacterial endocarditis due to *Streptococcus viridans* or *fæcalis*, although if these larger doses of penicillin, or the combination of penicillin and streptomycin, prove ineffective, aureomycin or chloramphenicol should be tried if *in vitro* studies show that the infecting organism is sensitive.

STREPTOMYCIN

Attempts to counter the toxic effects of streptomycin on the vestibular mechanisms (i) by antihistamine drugs, and (ii) by limiting the dosage to 1 g. daily in the adult, which, whilst therapeutically adequate, is unlikely to cause marked nausea, vertigo, ataxia or deafness, have not been wholly effective. It is moreover doubtful if the earlier claims, that dihydrostreptomycin is significantly less toxic than streptomycin, can be sustained (Carr *et al.*, 1950). Because of its toxicity and the rapid development of resistant strains of organisms, streptomycin is being supplanted in most infections by the newer antibiotics. It still remains, however, the antibiotic of choice in tuberculosis and, alone or in combination, in urinary tract infections due to *Pseudomonas aeruginosa* and *B. proteus*, and in enterococcal endocarditis.

Preliminary studies on *neomycin*, isolated by Waksman and his associates from *Streptomyces fradiæ*, suggest that it has an effective spectrum similar to that of streptomycin (Kadison *et al.*, 1951). It is potent in infections caused by salmonella, pseudomonas, escherichia, aerobacter, klebsiella, and proteus; and in extrapulmonary tuberculosis. In pulmonary tuberculosis and brucellosis its effects were not encouraging. It has toxic actions, similar to those of streptomycin, on the vestibular apparatus and on the kidneys, and the production of resistant strains during treatment has been noted.

Another antibiotic with a proportionately high activity against *Mycobacteria*, including the tubercle bacillus, is *viomycin*, obtained from *Streptomyces punicus* and *Streptomyces floridæ*. A recent series of reports in the *American Review of Tuberculosis* indicates that *in vitro* it is effective primarily against acid-fast bacteria, including strains of tubercle bacilli which are resistant to streptomycin, neomycin and *para*-aminosalicylic acid (PAS). These studies showed that in man it has similar toxic effects to streptomycin, and suggested that its place in therapy would at best be limited to those patients infected with strains of tubercle bacilli resistant to other agents.

CHLORAMPHENICOL, AUREOMYCIN, TERRAMYCIN

It is with these three antibiotics that most reports have dealt in the past year. *Chloramphenicol* is now available in this country through the National Health Service, and it is a striking commentary on the expense involved when a new antibiotic is released for general use that in the first seven weeks of its release from December 9, 1950, to January 31, 1951 (which, it is true, included an influenza epidemic), the cost of this drug, dispensed by retail pharmacies for the N.H.S., was £350,000! *Aureomycin* is available

from special centres for designated infections. *Terramycin*, produced from *Streptomycin rimosus*, is not yet obtainable in this country; from both pharmaceutical and therapeutic standpoints terramycin resembles aureomycin more closely than chloramphenicol.

These three antibiotics have many common features and with few exceptions are equally effective in the treatment of susceptible infections. Their outstanding characteristics are (i) low toxicity, (ii) effective control of a broad spectrum of infective agents, and (iii) adequate absorption from the digestive tract, so that they can be given by mouth. A single oral dose of 1 g. gives an effective therapeutic blood level for twelve hours or more, but if oral medication is contraindicated, aureomycin can be given intravenously in about half the oral dose, though it should be well diluted.

The total daily oral dose for all three antibiotics is 2 to 4 g., in equally divided doses, every four to six hours. In contrast to penicillin their action is bacteriostatic rather than bactericidal, hence the relatively poor results from chloramphenicol and aureomycin in the treatment of subacute bacterial endocarditis, although the causative organisms are highly susceptible *in vitro*. Their *in vitro* and *in vivo* responses are not always parallel, e.g. *S. typhosa* is highly susceptible to both chloramphenicol and aureomycin *in vitro*, but chloramphenicol is vastly superior in the treatment of typhoid fever.

The infections in which these three antibiotics play a special part in contrast to penicillin are: the typhoid group; most coliform infections of the urinary tract except those due to *B. proteus* or *Ps. aeruginosa*; brucellosis of all types (though relapses are common); and most rickettsial infections, including typhus, Q fever and spotted fever. Susceptible virus infections are primary atypical pneumonia, psittacosis, lymphogranuloma inguinale; and possibly chancroid, herpes zoster and disseminated vaccinia. Among protozoal infections, amœbic dysentery often shows dramatic cure with aureomycin. Bacterial pneumonias which respond include streptococcal, pneumococcal, staphylococcal, influenzal, Friedländer's and tularæmic pneumonias. Cutaneous anthrax has responded well. Viral forms of gastro-enteritis seem unaffected and the response to salmonella infections is variable. In Shigella dysenteries the results are similar to those of the sulphonamides which, because they are much cheaper, are at present preferred. Despite early enthusiastic reports (Lassen and Grandjean, 1951), there is increasing doubt of the effectiveness of these antibiotics in the treatment of whooping-cough, and attention should be called once again to their ineffectiveness in such common infections as the common cold, viral influenzas, poliomyelitis, infective mononucleosis, fungoid infections, and rheumatic fever. But workers in this field are

> '..... ever reaping something new,
> That which they have done but earnest of the things that they shall do'.

The untoward effects of treatment with these antibiotics are singularly

few. Gastro-intestinal disturbances with anorexia, nausea, vomiting and epigastric pain may occur. These can be reduced, without lowering plasma levels of the drugs, by giving them in milk. Antacids of the aluminium hydroxide gel type interfere with the absorption of aureomycin from the gastro-intestinal tract and must be avoided. Monilial infections of the mouth with atrophic glossitis and 'black hairy tongue' may follow the destruction by antibiotics of the bacterial flora of the mouth which results in uninhibited fungal overgrowth, and the oft-described rectal and vulval irritation and burning are probably of similar origin (Woods *et al.*, 1951).

It has earlier been noted in discussing the treatment of subacute bacterial endocarditis that a combination of antibiotics has often proved most effective. This is true also of brucellosis; of certain staphylococcal infections in which both penicillin and aureomycin may be necessary; and in infections for which enterococci or gram-negative bacilli are responsible, there may be need for streptomycin and chloramphenicol. There is some experimental evidence that combined therapy may result in mutual interference, but no impaired activity due to this cause has been observed in man.

ANTIBIOTICS IN PROPHYLAXIS

The rôle of antibiotics in the prevention of disease is increasing. Dental extractions, tonsillectomies and other surgical operations, and parturition in complicated deliveries, are examples of procedures in which penicillin 'umbrellas' have greatly decreased morbidity and mortality, especially in the susceptible. The prophylactic value of penicillin in syphilis and gonorrhœa, and of chloramphenicol in scrub typhus, has been emphasized in recent reports, and there is suggestive evidence that not only is penicillin of value in preventing recurring attacks of rheumatic fever in known rheumatic subjects, but that rheumatic fever may be prevented by early and intensive therapy with penicillin after the onset of a streptococcal sore throat. These observations need confirmation, especially as it has been shown by Weinstein *et al.* (1950) that the treatment of scarlet fever with crystalline penicillin G does not prevent the development of rheumatic fever or glomerulonephritis as 'late' sequelæ.

Two points in prophylaxis are worth notice. First, that there is no need to give a penicillin 'umbrella' for several days before operation, as is the custom in many hospitals. It suffices to give penicillin a few hours before, so as to ensure the maximum concentration in the blood during the operation when infected tissues are being handled, and for forty-eight hours after operation, which adequately covers the possible systemic dissemination of organisms from the infected site. Surgeons will remember that asepsis is still to be preferred to antisepsis. Secondly, prophylactic doses of penicillin must be adequate. There is a real danger from the multiplication of resistant strains, and I suspect that in three of my cases of enterococcal endocarditis following parturition, the use of a penicillin 'umbrella' played an etiological part.

THE CHEMOTHERAPY OF TUBERCULOSIS

Large-scale trials and thorough follow-up studies are now available for the evaluation of the chemotherapeutic and antibiotic agents which give promise of improving the treatment of tuberculosis. All investigations emphasize the need for using them in conjunction with other established methods of medical and surgical management. Neomycin and viomycin have already been referred to and it is still too early to give them judical assessment. At a recent American conferenee (*Amer. Rev. Tuberc.*, 1951) what is almost certainly the largest number of carefully selected and controlled cases of tuberculosis in the history of the disease was analysed. More than 6000 cases were studied during their first course of treatment, and 2000 during subsequent courses. The view was generally held that streptomycin still remains the most effective agent, with *para*-aminosalicylic acid (PAS) a most valuable adjunct. This combination permits of streptomycin treatment being given to patients previously considered unsuitable. By delaying the emergence of streptomycin-resistant variants of tubercle bacilli it enables the period of effective streptomycin therapy to be prolonged; and by reducing the necessary dosage of streptomycin it limits the toxic hazards of its prolonged use. In combined therapy the effective initial dose of PAS was 12 g. daily for adults, with a dose of streptomycin of 1 g. every three or four days.

Much work has also been carried out on the thiosemicarbazones, especially *thiacetazone*. It can be given by mouth or parenterally in doses of 25 to 50 mg. daily for the first week or two, with a gradual increase to 200 to 300 mg. daily if the patient can tolerate it, and treatment can be continued for six to twelve months. It is said to give its best results in active early lesions of the lungs and in laryngeal and intestinal tuberculosis, but in general infections it is acknowledged to be far less effective than streptomycin. Moreover, toxic symptoms are common: gastro-intestinal upsets, headache, photophobia, skin reactions, granulocytopenia, purpura and hepatic necrosis have all been recorded. It is doubtful if thiacetazone will find a permanent place in the treatment of tuberculosis.

STREPTOKINASE AND STREPTODORNASE

Nearly twenty years ago, Tillett and his associates showed that from broth cultures of *beta*-hæmolytic streptococci (Group A) a lytic factor could be isolated which rapidly liquefied human fibrin clots. Further investigation showed that this lytic principle was, in part, a catalyst which activated a fibrin-lysing system in the euglobulin fraction of human serum—*streptokinase*; and, in part, the enzyme, desoxyribonuclease, which was given the name *streptodornase*. Both these are without effect on living tissues, so they can be used to bring about the hydrolysis of fibrin and desoxyribonucleoprotein, if they can be brought into direct contact with fibrin or pus for a sufficiently long period. They thus tend to eliminate conditions which favour infection, and facilitate the formation of healthy granulation tissue

(Miller *et al.*, 1951). Not only is this of value in surgery but in medicine also, e.g., by the hydrolysis of fibrin in a clotted hæmothorax.

HYALURONIDASE

Two years ago Gaisford and Evans (1949) reported on the use of hyaluronidase, an enzyme which acts on connective tissue, rendering it more permeable, as an aid to the parenteral administration of fluid to infants and children. Since the difficulties of the intravenous route at an early age are often insurmountable, this method offered a useful alternative. Many reports followed suggesting that the method had varying efficacy. Gaisford and his co-workers (Evans *et al.*, 1951) have emphasized as possible causes of the differences: (i) the uncertain potency of the preparation used; (ii) the technique of the administration; and (iii) a failure to recognize the limitations of hyaluronidase. The conditions in which hyaluronidase has proved of special value are severe dehydration fever in the newborn, pyloric stenosis, and gastro-enteritis. The authors emphasize, however, that any seriously ill, toxic and dehydrated infant will need fluid intravenously, and that the value of hyaluronidase is that it minimizes the number of intravenous infusions which may be required.

CORTISONE AND ACTH

Among the systemic diseases which a year ago were regarded as responding favourably to cortisone were rheumatic fever, rheumatoid arthritis, psoriasis, disseminated lupus erythematosus, polyarteritis nodosa, dermatomyositis, acute leukæmia, ulcerative colitis, bronchial asthma, and urticaria. Further studies have shown that except for rheumatic fever and rheumatoid arthritis (i) the response in the others occurs in only a proportion of patients; (ii) remissions thus induced are often of short duration and may be symptomatic only, e.g., in acute leukæmia, in which despite improvement in the general condition and in the blood picture the marrow may remain unaltered; (iii) relapses are often resistant to further treatment; and (iv) complications may follow treatment, e.g. perforation in ulcerative colitis and in peptic ulcer, and dissemination of tuberculosis. There is increasing support for the oft-quoted opinion that, 'ACTH and cortisone do not cure anything', although it seems premature to regard them simply as 'glorified aspirin'. They are most powerful instruments of research on the tissue reactions in disease, and have demonstrated beyond doubt the potential reversibility of rheumatoid arthritis, rheumatic fever and carditis, disseminated lupus erythematosus, polyarteritis nodosa, some forms of iridocyclitis, and certain allergic states in particular. It has indeed been found possible by using initial large suppressive doses, followed by gradual reduction, to secure adequate control of rheumatoid arthritis in about 64 per cent. of cases (Boland, 1951). The ability to maintain satisfactory improvement varies in general indirectly with the severity of the arthritis.

In about half the cases serious signs of hormonal excess appear, which demand such a reduction in dosage that clinical deterioration in the arthritis follows. These toxic effects include a tendency to Cushing's syndrome with hypertension; glycosuria and occasionally mild diabetes mellitus; a negative nitrogen balance; hypertrichosis; acne; œdema due to sodium retention which can precipitate cardiac failure; menstrual disturbances; osteoporosis with spontaneous fractures; psychotic disturbances, usually of elation and euphoria, but occasionally of severe depression; frequent electro-encephalographic changes (Hoefer and Glaser, 1950); and the inhibition of the natural processes of healing in ulcers and wounds. In certain types of inflammation, e.g. beryllium poisoning, the beneficial effect of cortisone may well be of great importance (Kennedy *et al.*, 1950).

Thus, as experience grows, the limitations, difficulties, and dangers of ACTH and cortisone therapy in chronic disease are becoming increasingly evident, although of their value in certain types of acute and subacute arthritis and iritis, and as a research tool, there can be no doubt. What the year has taught is that whatever be the ultimate rôle of drug therapy in the treatment of rheumatoid arthritis we ignore at our patients' peril the help to be gained from physiotherapeutic and orthopædic measures, both in its treatment, and in the prevention and correction of crippling deformities.

The supply of ACTH and cortisone, though increasing, is still far short of the demand. Fresh sources of pituitary glands and bile are being used, and many plants including the Mexican wild yam, the tomato and even the potato, have been explored in the past year as possible sources of those phenanthrene-ring products which might be convertible into adrenal steroids. But the processes are complex, and so efforts have been made to find a substitute for cortisone. These are twofold. One has been an attempt to produce a cortisone-like action with related and more easily obtainable steroids, e.g. DOCA and pregnenolone. Although earlier reports on the combined use of DOCA and ascorbic acid in rheumatoid arthritis were favourable, carefully controlled studies have failed to confirm these, and it has been shown that no steroids other than compound F reproduce the action of cortisone. The other has sought to find a substance of quite different chemical composition which yet might resemble cortisone in its effects, in the same way that stilbœstrol, chemically quite different from naturally occurring œstrogens, has, nevertheless, similar biological actions. It was not surprising that salicylates should be regarded as possibly having a basically similar action to cortisone, for in rheumatic fever both reduce pain, fever, and sedimentation rate, and both increase uric acid excretion. Moreover, some observers suggest that salicylates resemble cortisone in causing water retention followed by diuresis, in raising the blood sugar level, and in causing acne and a modified Cushing's syndrome (Reid, 1951a). A new salicylate compound—sodium γ-resorcylate—is said to be even more effective (Reid *et al.*, 1951b), but judged by Sayer's test (ascorbic acid de-

pletion in the adrenals), the effect on circulating eosinophils in man, and the therapeutic response, the balance of evidence is against salicylates and related salts having an adrenocorticotrophic action.

A cinchonic acid derivative—3-hydroxy-2-phenylcinchonic acid (H.P.C.)—was tried by American workers (who had shown that the drug administered to the rat with an intact pituitary reduced the ascorbic acid content of its adrenal) in a series of cases of collagen diseases, and Rennie *et al.* (1951) reported on its trial in Glasgow. They found that fever and acute arthritis were rapidly relieved in rheumatic fever, but the results in polyarteritis nodosa and disseminated lupus erythematosus were inconstant. On the other hand they claimed that striking benefit was obtained in three patients with scleroderma, although this proved only temporary in two. Toxic effects included slight nausea, diarrhœa, and more rarely vomiting; liver damage was not observed. No claim is made that the drug has a cortisone-like action, although this should easily be capable of experimental demonstration.

A hint, though no more than a hint, of a simple substance which may be the solution to the mode of action of cortisone comes from the work of Long and Miles (1951). It is suggested that cortisone facilitates the oxidation of ascorbic acid to dehydroascorbic acid and that it is this latter substance which may be responsible for the cortisone action.

None of the proposed substances are likely to displace ACTH and cortisone. If saving is to be secured while supplies are limited, we must seek the most effective and economical methods of administration. Recent work from several centres claims that ACTH by intravenous drip is not only free from the hazards of anaphylaxis (though contrary experiences have been noted), but that it is more effective than intramuscular injection. Indeed, slow intravenous infusion is said to be twenty times more potent than intramuscular injection of the same amount of the drug.

THE ANTIHISTAMINES

Shortly after the antihistamine drugs were introduced an encouraging report on their effectiveness led to their widespread use in the prevention and treatment of the common cold. Indeed, the *Reader's Digest* published an article under the provocative title, 'Is This, at Last, Good-bye to the Common Cold?' The answer to this compelling question has been given in the past year by several carefully controlled investigations which have shown beyond any doubt that, whatever be the antihistamine drug used, the treated are no better off than the controls in the incidence, severity of symptoms, or duration of colds (Feller *et al.*, 1950; Hoagland *et al.*, 1950). Yet an uncritical public continues to demand them, confirming Andrewes' observation that 'even the most eminent men of science almost invariably lose all sense of critical judgment where colds, especially their own colds, are concerned, and the statistical methods they use in their daily work are all forgotten'. Reliable estimates suggest that in the United States the total sale of these drugs reached $100,000,000 in 1950. When properly prescribed under medical supervision for allergic states, Parkinsonism, Ménière's syndrome and sea-sickness, toxic effects are infrequent, but there is increasing

evidence of the dangers of self-medication which appear to be too little known. Several fatal cases have been recorded, especially in children in whom there is a predisposition to convulsions. Psychotic changes are common, and agranulocytosis has been observed with an occasional death.

SMOKING AND CANCER OF THE BRONCHI AND LUNGS

The striking increase in the incidence of cancer of the bronchi and lungs in this country, as shown by the Registrar-General's figures (fifteenfold between 1922 and 1947), reflects similar trends in the United States and elsewhere. Among the factors held to play a part, largely on the theoretical basis that irritants are carcinogenic, have been (i) the increasing atmospheric pollution from petrol fumes and motor car exhausts, from gas works and tarred roads, and from the smoke of coal fires and industrial plants; and (ii) from tobacco smoking. Many papers have, in the past, recorded strong circumstantial evidence that cigarette smoking is a factor in the etiology of cancer of the respiratory tract, but not until the past year have careful statistical studies given unequivocal support to this view.

The American observers, Wynder and Graham (1950), studied 650 men with bronchogenic carcinoma. Of these, 96.5 per cent. had smoked over ten cigarettes per day for more than twenty years as compared with 73.7 per cent. of a similar group without cancer; and 51.2 per cent. had smoked over twenty-one cigarettes per day as compared with 11.1 per cent. in the general hospital group. In their series only 2 per cent. of cases of cancer of the lung occurred in those smoking less than four cigarettes per day. They found that there might be a lag period of ten or more years between the cessation of smoking and the onset of symptoms of lung cancer, and they explain the male preponderance in this disease by the fact that few women have smoked for as long a period as twenty years. Clearly, if this view is sound and smoking is as important as they suggest in the etiology of lung cancer a significant increase in women may be observed as the years pass. Doll and Bradford Hill (1950) have confirmed in general these findings and have reached the speculative conclusion that among the population of London over the age of forty-five those who smoked twenty-five or more cigarettes a day were fifty times more likely to develop cancer of the lung than non-smokers of the same ages! Their findings do not lend support to the opinion of the American workers that 'inhaling' is an aggravating factor.

The nature of the carcinogenic agent is left open. There is no evidence that potent carcinogens, e.g. benzpyrene, are formed in the combustion of tobacco, nor that insecticides containing arsenic and used in spraying the tobacco plants provide an explanation of the association of tobacco smoking and cancer of the lung. Petrol lighters and cigarette paper have been indicted by some without adequate evidence. It is clear that the full elucidation of the problem will need much more research—clinical, statistical and experimental. In the meantime, economic factors rather than its potential carcinogenicity are likely to result in the diminished use of tobacco.

ALCOHOLISM

The suggestion has been made that in alcoholism, deficiency of the adrenal cortex may be constitutional or the result of the prolonged and excessive

intake. In either event the administration of adrenal cortical extract (ACE) might be expected to benefit the victim.

Smith (1950) reports on the effect of both ACTH and ACE in Korsakoff's psychosis, acute alcoholic intoxication, and delirium tremens. No sedation or supportive measures were given but each patient received 25 mg. of ACTH (or ACE) intramuscularly at intervals of six hours. The results were dramatic. Treated by conventional methods the patient with delirium tremens recovered in forty-eight to seventy-two hours; with ACTH recovery occurred in three to ten hours.

Both ACE and ACTH are effective in the treatment of acute alcoholic intoxication; in delirium tremens ACTH is the most dramatic treatment yet known; ACE is effective in Korsakoff's psychosis, whilst ACTH is not. In the chronic alcoholic the effects are not so satisfactory. Thimann (1951) reports that ACE was administered to 22 patients, and of these only 6 maintained uninterrupted abstinence over an observation period of two to nineteen months. This is approximately the same proportion responding to 'antabuse', about which disquieting reports of toxic effects, some fatal, are beginning to appear. Some of these are nervous—headache, drowsiness, ataxia, retrobulbar neuritis; toxic erythemas are frequent; but the major risk lies in circulatory collapse, rendering the patient pulseless, cyanotic and unconscious, following even moderate amounts of alcohol ($\frac{1}{2}$ to 1 ounce whisky) while on the drug.

THE BEDPAN AND THE COMMODE

In our preoccupation with the more dramatic and direct methods of attack on disease we should not overlook those apparently minor procedures which may contribute to a patient's burden. Almost universal habit has resulted in severely ill patients being subjected to the mental indignities and the physical discomforts and strain of the bedpan even though, as in many cardiac and respiratory diseases, mobility is unimpaired.

Many physicians who have revolted against the bedpan habit will be encouraged by the careful investigation of Benton *et al.* (1950), who showed that, in a group of 13 non-cardiac and 15 compensated ambulant cardiac subjects, energy expenditure in terms of oxygen consumption above resting levels was consistently higher on the bedpan than on the commode (50.7 per cent. for the cardiac group, and 48.4 per cent for the non-cardiac), which is statistically highly significant.

McGuire and his colleagues (1950) discuss the causes of death of 11 patients who had died on the bedpan. Although in some, as for example in pulmonary embolism, the call to stool may be an agonal reflex, in others there is little doubt that straining at stool imposes undue circulatory strain, and may give rise to dissecting aneurysm, subarachnoid hæmorrhage, myocardial infarction and pulmonary embolism. As soon as straining begins the blood pressure rises and the pulse slows, but as straining is maintained the blood pressure falls to levels well below normal, and this fall is aggravated by relaxation. These and later fluctuations may precipitate intravascular clotting and dislodge venous thrombi.

ABUSE OF BED REST

Wells (1950) emphasized in his surgical contribution to this symposium a year ago how slowly the doctrine of early postoperative ambulation was spreading. In medicine, the slavish adherence to ritualistic tradition as earlier illustrated by the bedpan is as common a fault. In peptic ulcer, for example, medical treatment often comprises a regime in which the period of rest in bed, intervals between feeds, and additions to the variety and amount of food follow an invariable and inviolable pattern whatever the site or size of the ulcer. The same holds for myocardial infarction. A set regime of bed rest of four to six weeks is often ordered which pays little regard to the size and position of the infarct. The disadvantages of recumbency—the poor circulation to the lung bases, the increased predisposition to thrombophlebitis and resulting embolism, the abnormal nitrogen and calcium metabolism, and particularly the economic factors and psychogenic sequelæ—are all adduced by Irvin and Burgess (1950) as evidence that routine prolonged bed rest is not only unnecessary, but potentially harmful to the mental and physical well-being of patients. Although they recognize the need for individualization in therapy, and that in patients with extensive infarction modifications will be necessary, they advise that for the majority of patients a rest of two weeks in bed, and bed-side toilet privileges, suffice. If all is then well patients should be gradually allowed to walk longer distances, until at the end of four weeks from the onset they have regained some of their previous exercise tolerance and are prepared to leave hospital on light activity.

These recommendations are essentially opinions. The authors confess that relevant and statistically valid facts are few, but there would appear to be little doubt that in most cases the period of bed rest in myocardial infarction can be shortened with advantage and safety.

CONCLUSION

Only the major achievements in therapy during the past year can be mentioned in this brief survey. Many of the gaps will be filled by the special contributions to this symposium. Moreover, nothing has been said of several drugs with reputations once bright that have become clouded, such as vitamin P and rutin in hæmorrhagic disorders, methonium compounds in hypertension and peptic ulcer, the sulphonamide drugs and antibiotics in ulcerative colitis, the nitrogen mustards and aminopterin in leukæmias and reticuloses, and a host of others.

Time and again evidence has been forthcoming that the solution of a problem has created a fresh problem, as is shown by novel pictures of disease, by changes in its incidence and economics, and the toxic manifestations of many new remedies. These make it imperative to stress once again that although the public is rightly entitled to receive the benefits of new discoveries as early as possible, they should not be exposed to the

risks of being the victims of uncritical enthusiasms, nor of inadequately tested remedies, which may carry serious hazards.

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ADVANCES IN SURGERY

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THE advances in surgery and in its correlated fields since the first number of *The Practitioner* appeared in 1868 have made a conspicuous era in the history of medicine. These advances have been based largely upon the application of the fundamental principle of coordinating the medical sciences (anatomy, pathology, bacteriology, physiology, and biochemistry) with clinical practice and investigation. In recent years this coordination has been evident in the development of certain epoch-making contributions to the art and science of surgery, and has set a pattern which will determine the course that surgery will follow in the years to come.

ANÆSTHESIA

In the fields which have transformed surgery within the past century, namely, anæsthesia and antisepsis, progress has been dramatic; and new fields of surgery have been made possible, especially surgery of the lungs, the heart, and the central nervous system. The establishment of departments of anæsthesiology in teaching hospitals has led to intensive investigations of the properties of new anæsthetic agents, of new preparations for supportive therapy, and of new methods of administration. These have led in turn to the development of methods of balanced anæsthesia in which specific indications for various anæsthetic agents are combined to meet the requirements involved in the condition of the patient and the increasing complexity of surgical procedures. A method which is eminently satisfactory to both surgeon and patient and has a wide range of application, utilizes curare, which makes possible adequate anæsthesia with intravenously injected pentothal sodium, together with the administration of 50 per cent. nitrous oxide and 50 per cent. oxygen through a Magill intratracheal tube, an instrument which has proved a great boon to successful and safe anæsthesia.

One of the most important contributions of anæsthesiology has been in the diagnostic and therapeutic nerve blocks under radiological observation for the determination of pain paths. As Lundy has pointed out, this method will aid in determining whether a patient should be given injections of 'dolamin' or of alcohol; whether X-ray therapy should be employed; whether a nerve, or perhaps more than one nerve, should be cut; whether chordotomy or even prefrontal lobotomy should be performed; or whether the patient is of a type which probably will respond poorly to any treatment.

CHEMOTHERAPY

In the prevention and treatment of surgical infections, chemotherapy has

already written a chapter in the history of medicine comparable in its benefits to mankind to the era of Lister and Pasteur. Following the pioneer work of the Oxford group (Florey and associates) the bactericidal properties and therapeutic indications of the *antibiotics* have gradually evolved. The general principles governing their use in surgery have recently been summarized by Pulaski: (1) sensitivity of bacteria to chemotherapeutic agents; (2) nature of lesions; (3) duration of contact between bacteria and antimicrobial agent; (4) adequacy of dose and duration of its administration; (5) resistance of host; (6) possible alteration of bacterial flora during antibiotic therapy; and (7) toxic reactions.

Pulaski has emphasized the necessity of the pre-treatment isolation and culture and sensitivity testing of the causal organisms, although examination of the direct smear can yield invaluable aid in clinical diagnosis. The haphazard use of antibiotics in unexplained fever or pain should be thoroughly condemned; but, as Herrell has pointed out, therapeutic trials are on occasion justified if all efforts to establish accurate bacteriological diagnosis have been exhausted. The increase of penicillin-resistant strains of *Staphylococcus aureus* is noted by all observers, but they also agree that the resistance of other microbes to penicillin has been exaggerated and over-emphasized. A high percentage of gram-negative as well as gram-positive cocci are sensitive to aureomycin, chloramphenicol (chloromycetin), and terramycin, although it is already known that certain microbes will become, and can be made, resistant to these agents.

Chemotherapy, to be effective, must be combined with free drainage of cavities; and invasive or spreading infection will resolve with little or no necrosis if the appropriate antibiotic be given early. In general, the antibiotics are most effective in acute infections, characterized by cellulitis. In postoperative infections of the respiratory tract following massive collapse, aspiration, and trauma, prompt diagnosis, bronchial aspiration, and reaeration of lung together with chemotherapy will usually correct atelectatic pneumonia in a few days. Under such conditions, aureomycin, terramycin, and chloramphenicol are preferable to penicillin. In wound suppuration, antibiotics cannot replace the employment of sound surgical practice. Antibiotics are inert in acute cholecystitis and empyema of the gall-bladder because of the obstruction present. Similarly, in conditions when there is little or no blood supply, for example, gangrene or large abscess, few if any beneficial effects can be expected from their use.

The advantages of the overlapping activities of the various antibiotics in certain fulminating infections and in acute infection have been established, but full doses of any combination of antibiotics should be used initially. In this combination therapy it is now known that certain of these combinations may be undesirable rather than beneficial, since some antibiotics antagonize rather than complement each other. In spite of the wide use of antibiotics for prophylaxis against infection, few controlled studies for determining their usefulness have appeared, but the evidence of their protective

properties is recognized, particularly in intestinal bacteriostasis, in the surgery of tuberculous lesions, and in the fact that no patient with an organic heart murmur should undergo oral, transurethral, or intestinal surgery without the benefit of preoperative prophylactic antibiotic therapy. The routine use of antibiotics, however, is not justified, and they will not compensate for careless technique or disregard of surgical principles, for, as Sir Alexander Fleming, to whom the medical profession owes an eternal debt of gratitude for the discovery of penicillin, has well said, 'Antibiotics simply attack the bacteria; the surgeon must treat the patient'.

Pulaski attributes failure to obtain effective results to the use of the wrong antibiotic or drug, resistance or inadequate dosage, added infection, or far-advanced disease, debilitation of the patient (failure to treat the patient as a whole), inaccessibility of the lesion to antibiotics and, above all, blind reliance on antibiotics as a substitute for established, time-honoured surgical principles.

SURGERY OF CANCER

In the surgical treatment of cancer in its various situations, definite advances have been made: in the earlier recognition of the disease through education of the profession and the public; in extension of the scope of surgery in dealing with cancer in situations heretofore considered inaccessible, and in more extensive surgical procedures; in steadily decreasing surgical mortality, and in raising both the operability rate and the prospects of cure. The alertness of the profession in the past few years in thoroughly investigating signs and symptoms which might indicate early malignant lesions is encouraging, since the first objective is an early diagnosis. In this connexion, a most important contribution has been in the cellular differentiation in secretions which have been in contact with the lesion. For example, when such a diagnostic method is used by skilled observers, it is found that in 80 per cent. of cases of carcinoma of the lung, cancer cells can be demonstrated in the sputum (in some instances when radiological evidence is absent), and that cancer cells can be demonstrated in a high percentage of cases of non-infiltrative cancer of the cervix; but the method is as yet of little value in cancer of the kidneys and urinary tract, and in cancer of the stomach its value is limited to cancer of the cardia when direct smears are examined at the time of œsophagoscopy.

The progress in the development of surgical management of lesions of *the œsophagus* since the pioneer work of Grey Turner is a tribute to the place of roentgenology and endoscopy in the early recognition of these lesions, and is represented in the present resectability rate in cancer of the œsophagus of 65 per cent. (of the patients on whom exploration is performed), and a mortality rate of 7 per cent. An even more remarkable example of the achievements of present-day surgery has been the success reported in the repair of congenital œsophageal atresia and tracheo-œsophageal fistulæ.

Cancer of the gastro-intestinal tract appears to be relatively static in

respect to operability rate and curability. However, in cancer of *the stomach* the more frequent use of total gastrectomy may add to the percentage of cures, although the sequelæ of the operation are a matter of concern. The present status of cancer of the stomach is a dismal one, for it is still true that in 50 per cent. of the patients seen the lesions are found to be inoperable on examination; in 50 per cent. of the cases in which exploration is performed the lesions are resectable; and 30 per cent. of the patients from whom the lesions are removed will live five years, although the five-year survival rate when lymph nodes are not involved is about 50 per cent. The lesson in this is obvious.

In cancer of *the colon*, the most conspicuous advances have been in the more frequent employment of one-stage operations in the lower part of the rectosigmoid, and in the extraordinary safety with which such lesions can be removed with the protection against infection afforded by antibiotics. Resections of malignant lesions of the colon carried out in 1950 at the Mayo Clinic show a mortality rate of less than 2 per cent. in 562 cases.

Pneumonectomy for cancer of *the lung* has become a routine procedure but is another evidence of the remarkable achievements possible today with coordinated approach to any surgical problem. The present operability rate of cancer of the lung is approximately 50 per cent. (70 per cent. of those on whom exploration is performed); the mortality rate is 5 per cent.; and the five-year survival rate is about 80 per cent. in the squamous-cell type.

The persistent search for factors involved in the development of cancer is illustrated in the work of Huggins on cancer of *the prostate*. His investigations show that human prostatic cancer is stimulated by the administration of androgens, and depressed by measures whereby the androgens are controlled; and he has demonstrated that prostatic cancer is the first example of widespread carcinomatosis in which endocrine therapy has had a beneficial effect.

CARDIAC SURGERY

In sharp contrast to surgery in cancer, there have been the spectacular developments in the surgery of the heart and great blood vessels, for the approach to this problem has been through the experimental laboratory. The achievement of successfully correcting the congenital anomalies of *patent ductus arteriosus*, the tetralogy of Fallot and coarctation of the aorta, will be recognized in the history of surgery as one of the great triumphs of this era. The recent procedures devised and carried out on *mitral stenosis* enter a realm in which modern surgery has already accomplished startling and most promising results. The method of cutting the stenosed mitral valve by dividing the commissure with a knife edge carried on the finger introduced through the left auricular appendage can be accomplished with a mortality rate of 5 per cent., and results up to the present are found to be excellent in 50 to 80 per cent. of cases In view of the crippling nature of mitral stenosis and its relatively frequent occurrence, the significance of the place of surgery in this and other cardiac conditions is obvious.

PANCREATECTOMY

Surgical advances are well illustrated in the development of our knowledge of diseases of the pancreas, for example, that conservative treatment is preferable to radical treatment in acute pancreatitis. The spectacular cures of hyperinsulinism by removal of islet cell tumours, and the partial or total extirpation of the pancreas, represent an epoch-making achievement. To have shown, for example, that total pancreatectomy for hyperinsulinism can be performed and the patient remain well without substitution therapy other than insulin over a period of five years may be the forerunner of more frequent surgical intervention in pancreatic carcinoma. In this, Whipple and his associates in their experimental and clinical investigations made possible the opening up of a field of definite possibilities.

PORTAL HYPERTENSION

The present status of surgical treatment of portal hypertension is somewhat uncertain. Although it is a formidable procedure, it has been shown that various types of shunting operations can be safely carried out and that in selected cases, chiefly those in which hepatic damage is not too great, protection can be afforded against the complication of hæmorrhage; but not enough time has elapsed for a definite appraisal of the ultimate effect of the operation. However, in preventing fatal hæmatemesis some spectacular results in individual cases in which bleeding had occurred repeatedly provide strong evidence that such protection is real.

THYROID, PARATHYROID AND ADRENAL GLANDS

The place of surgery in diseases of *the thyroid* has become somewhat modified through the use of radioactive iodine in the diagnosis and treatment of thyrotoxicosis and cancer of the thyroid, and this method has contributed definitely to the remarkable safety with which operations on the thyroid can now be carried out. *Hyperparathyroidism* is one of the most important and interesting surgical conditions, since the diagnosis can now be established with considerable certainty by estimations of calcium and phosphorus in blood and urine, under carefully controlled conditions, even in cases without changes in the bones or urinary calculi. Even in such circumstances surgical exploration of the parathyroids is called for in anticipation of finding hyperfunctioning parathyroid tissue.

The adrenal glands present many fundamental surgical problems. The dramatic results following removal of an adrenal tumour in Cushing's disease are well known, and some recent investigations of the effect of resection of a hyperplastic adrenal gland in this disease are of interest in drawing the attention of the profession to the importance of early recognition of this syndrome. Again, current studies of the effect of total adrenalectomy in hypertension illustrate the advances made in knowledge of replacement therapy in the surgery of the adrenals.

PEPTIC ULCER

Peptic ulcer, particularly duodenal ulcer, is still associated with many unsolved problems. The primary question, of course, concerns the complexity and relative importance of the factors involved in producing a peptic ulcer, and of the factors responsible for its becoming chronic. The acid factor is apparently the predominant one but, in evaluating this factor, Ogilvie has pointed out that 'we must look for the cause of ulcer, not in the fact that the gastric juice contains acid, but in some increase in the digestive power of the juice, some disturbance in the normal relation of secretion to meals, or some failure in the protective mechanism'. Whatever further investigations will disclose in answer to these functional questions, the present status of the treatment of peptic ulcer, both medical and surgical, rests primarily on the sufficient reduction and control of acid to bring about healing in the unremoved ulcer and, more important in surgical treatment, to prevent recurrence. In this connexion, Ogilvie has properly questioned the advisability of extending this principle to the point of producing permanent achlorhydria by *radical gastric resection*. As he says, 'Patients with achlorhydria are often symptomless, but they have lost one phase of normal digestion, they have lost the bacterial protection of gastric juice, they are more prone than others to alimentary upsets and attacks of diarrhœa, and they are probably more prone than the average population to cancer of the stomach'. In addition, we know little about the ultimate effect of extensive gastrectomy on the general well-being and nutrition of such patients.

The introduction of *vagotomy* has added another tool which seems to be of great usefulness in recurrent ulcer after partial gastrectomy. The physiological effects of complete division of the vagi are such as to suggest combining the operation with gastro-enterostomy or pyloroplasty to compensate for the untoward after-effects of vagotomy. The late results of such multiple procedures cannot as yet be evaluated, but a recent preliminary report of a committee of the American Gastroenterological Association is of significance.

In 4000 cases of duodenal ulcer in which operation was performed by selected surgeons, 95 per cent. of the patients were clinically free from symptoms of ulcer following gastric resection, 96 per cent. following gastric resection plus vagotomy, and 71 per cent. following gastroenterostomy plus vagotomy. When, however, the results were compiled on the basis of whether or not the patient was satisfied with the operation, a slightly higher percentage of those who had undergone gastro-enterostomy plus vagotomy reported favourably (94 per cent.) than did those who had undergone gastric resection (93 per cent.). The recurrent ulcer rate (radiologically) was 1.6 per cent. for gastric resection and 2.4 per cent. for gastro-enterostomy plus vagotomy.

These statistical studies illustrate the difficulty of evaluating the over-all results of various surgical procedures and their combinations; for example, it is true that partial gastrectomy is a more positive method of controlling the acid factor than gastro-enterostomy, but recurrence of ulceration after partial gastrectomy is a much more serious problem, both for patient and surgeon, than recurrent ulcer after gastro-enterostomy.

This large series of cases will be re-studied later, cognizance being taken of the all-important time factor in estimating results, and careful inquiry being included into the habits of living to which patients return after operation.

The real advance in the management of duodenal ulcer has been, from the surgical standpoint, a negative one, for the indications for operation in duodenal ulcer are becoming less and less frequent as medical management becomes more and more effective. This change is borne out by the fact that surgical intervention in duodenal ulcer is carried out in approximately 12 per cent. of patients today in comparison with 40 per cent. only a few years ago.

One of the most perplexing questions about peptic ulcer concerns the management of *gastro-intestinal hæmorrhage;* but in massive hæmorrhage, definite progress has been achieved in the recognition that certain criteria call for surgical intervention, and that competent surgical treatment will save patients who would have succumbed to the hæmorrhage or its complications if non-surgical management had been continued. The general criteria on which surgical intervention seems to be indicated have been summarized by Crohn as follows:—

> An established diagnosis of ulcer, age of patient forty-five years or more, recurrent massive hæmorrhage while under observation, previous hæmorrhages, and the degree of severity of hæmorrhage (erythrocyte count less than 3,000,000 per cubic millimetre of blood, hæmoglobin less than 50 per cent.).

The non-surgical management of *perforation* has been advocated recently, and series of cases have been reported in which the recovery rate parallels that of surgical management. This is an important contribution, since circumstances may dictate that non-surgical management is safer for the patient than surgical intervention.

CONCLUSION

The general advances in all fields of surgery are chiefly in more accurate diagnosis, in which radiology and endoscopy play a major part, a clearer understanding of the indications for surgical management, the extension of the scope of surgical procedures, the continuing reduction in general mortality and morbidity rates as a result of better preoperative and postoperative care, more selective anæsthesia, and, above all, chemotherapy. The pursuit of these objectives through graduate and undergraduate training in surgery has been the motivating force in the advances in surgery. This progress has been based on the Hippocratic philosophy, exemplified in Lister, of experimentation, observation, and deduction—a philosophy which will determine the progress of surgery in the future.

ADVANCES IN OBSTETRICS AND GYNÆCOLOGY

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It is perhaps strange to attribute advances in treatment in obstetrics and gynæcology to experiences gained in the 1939-45 war, but such is, indeed, the case. The technique of, and indications for, blood transfusion became standardized, rhesus blood incompatibility became manifest, knowledge of the mechanism of oliguria and anuria in association with shock and hæmorrhage became clarified, and the place of chemotherapy and the use of the antibiotics in the various infective processes became established. Improvements in anæsthesia—both in the technique of administration and in the use of the less toxic anæsthetic agents—allowed of the performance of operative procedures of a magnitude previously considered impossible. All these advances influenced treatment, both in obstetrics and gynæcology, to a degree not yet fully appreciated, and credit must be given to those surgeons, anatomists, physiologists and biochemists who worked as a team as never before. Post-war advances have resulted largely from further research on those problems which arose during the war years. Much remains to be done, and the problem of the toxæmias of pregnancy still remains unsolved, although gradually more and more light is being shed on this subject.

ANTENATAL CARE

The aims of antenatal care remain unchanged, but a greater appreciation of the physiology of pregnancy and labour, and an understanding of the psychological requirements of the pregnant patient, have enabled the obstetrician to overcome many fears and prejudices. Mental and physical relaxation is encouraged, antenatal exercises are advocated, and the patient is enjoined to take a healthy and intelligent interest in her condition.

Routine blood investigations facilitate early treatment of syphilis, anæmias of pregnancy, and diabetes complicating pregnancy, whilst toxæmias of pregnancy are recognized at their onset by weight estimations, blood pressure readings, and urine analysis. The use of X-*ray pelvimetry* is practised as a routine in some clinics in an endeavour to assess disproportion, but it is still believed that clinical assessment is of the greatest importance. X-rays, however, can accurately assess the shape of a pelvis, and this is often of importance in determining the probable course of labour. The social and home conditions of the patient are investigated as never before, and the

early recognition of nutritional disorders allows of the appropriate treatment early in the pregnancy.

SEPSIS

Puerperal and post-abortal sepsis, once the most common causes of maternal morbidity and mortality, now rate below the hæmorrhages and toxæmias as causes of maternal death. The use of the sulphonamide group of drugs and the antibiotics has revolutionized treatment, whether the infection be of uterine, blood-stream, mammary, or urinary-tract origin. The range of such available drugs is so great that almost every type of organism is sensitive to at least one agent. The necessity for testing the organism's sensitivity to a particular antibiotic would appear to be obvious. The preoperative use of these agents in the presence of infection, or when infection is anticipated, has made for a security hitherto unknown in the treatment of septic incomplete miscarriages and in obstetric delivery after manipulation, whether the delivery be vaginal or abdominal.

HÆMORRHAGE

In 1939, in England and Wales, hæmorrhage associated with childbirth accounted for a mortality rate of 0.56 per thousand. By 1946 this figure had fallen to 0.33 per thousand. From antepartum hæmorrhage alone, over the same period of time, the mortality rate has fallen from 0.18 per thousand to 0.10 per thousand.

A review of the literature shows that up to 1945, *placenta prævia*, alone, was associated with a maternal mortality of 6 per cent., and a fœtal mortality which varied between 40 and 60 per cent. This was at a time when the accepted method of treatment for placenta prævia was immediate intervention when diagnosis was established. This often resulted in operative interference when the mother's condition was serious and the fœtus premature. In 1945, Macafee in this country and Johnson in America, working independently, advocated expectant treatment in certain cases of placenta prævia in the hope that the infants would reach greater maturity. This has resulted in a marked diminution in the neonatal mortality. Expectant treatment with a somewhat increased use of Cæsarean section, together with the greater use of blood transfusions, should reduce the maternal mortality rate to under 1 per cent. and the neonatal mortality rate to somewhere between 10 and 15 per cent. In some clinics these figures have been attained. The expectant treatment demands hospitalization of the patient for varying periods, an ever-ready operating theatre, and an adequate blood bank with transfusion facilities. Vaginal examinations should be avoided in all patients with antepartum hæmorrhage, except when facilities for Cæsarean section and blood transfusion are immediately available. The use of de Ribes bag, Willet's scalp forceps and the performance of version with withdrawal of a leg have been abandoned, although the last mentioned may be employed if the fœtus be dead. If intervention for placenta prævia be demanded, artificial

rupture of the membranes or Cæsarean section are the modern routine procedures, and the choice is dependent upon the type of placenta prævia encountered. Recently, Stallworthy (1950) has described the high posteriorly situated placenta prævia as the 'dangerous placenta', in that its presence in front of the sacral promontory produces a clinical disproportion with a high head. Rupture of the membranes in such cases fails to control the hæmorrhage, and Cæsarean section is indicated even though the placenta in no way encroaches upon the internal os.

With *toxic accidental hæmorrhage* from a normally situated placental site, associated with toxæmia of pregnancy or with hypertension, or both, the treatment depends upon the severity of the blood loss, the degree of shock and toxæmia exhibited, the efficiency of renal excretion, and the maturity of the fœtus. The modern trend is towards conservatism in such cases, in the knowledge that safe vaginal delivery is possible in most patients. Artificial rupture of the membranes with the use of pitocin is usually effective. The modern tendency is to treat each patient individually, and most authorities believe that Cæsarean section may be indicated if the toxæmia be of acute onset or if the placental separation be judged to be complete. The treatment of oliguria or anuria which is sometimes associated with toxic accidental antepartum hæmorrhage, especially if the hæmorrhage be concealed, has been greatly facilitated by the work of Bull and his co-workers. Instead of administering large quantities of fluids which the kidneys cannot excrete, only 1000 to 1300 ml. of intravenous glucose are administered in each twenty-four hours. Salt intake is limited, protein intake is markedly restricted, but fats in the form of peanut oil or butter are given.

It is now appreciated that in most, but not all, *postpartum hæmorrhages*, mismanagement of the third stage of labour is the cause. Attempts at expression of the placenta before it has separated must be avoided in the absence of bleeding, and the use of the newer anæsthetic agents has diminished the incidence of uterine atony. The administration of 0.25 mg. of ergometrine intravenously when the head or anterior shoulder is delivered has shortened the third stage and materially diminished blood loss. Manual removal of the placenta, provided the patient's general condition is good, has proved to be less dangerous than was previously thought, but this should not be attempted in the shocked patient until restorative measures have improved the condition usually associated with hæmorrhage, as well as shock. Ergometrine administration is useful (0.5 mg. intramuscularly, or 0.25 mg. intravenously) in all atonic uteri.

In all cases of hæmorrhage, whether these be ante- or post-partum, the patient's blood group and *Rh factor* estimation should be ascertained and transfusion resorted to when necessary. Cross-matching must routinely be employed, and if it is urgently necessary to administer blood, and if grouping facilities are not available, Rh-negative group O blood should be used, but direct cross-matching must be resorted to before transfusion begins.

TOXÆMIA OF PREGNANCY

As the actual cause of pregnancy toxæmia is unknown, treatment is of necessity somewhat empirical. However, many old concepts have been abandoned in the light of modern research work. All are agreed that rest, adequate sleep and freedom from worry are essential factors in the management of such patients. Furthermore, it is proved that salt intake must be markedly reduced, and the diet should contain not more than two grammes of sodium chloride daily. If this be adhered to there would appear to be no reason to restrict fluid intake, or indeed to increase it. The use of diuretics finds favour with some if œdema be present. Ammonium chloride is probably the safest, but opinion is divided over the use of mercurial diuretics. If oliguria or anuria be present, suggesting renal cortical necrosis, the special measures advocated by Bull and his co-workers already outlined (p. 352) must be implemented.

If *hypertension* be marked, bed rest and freedom from worries are probably the most important therapeutic measures, although the administration of hexamethonium bromide or allied compounds may prove helpful. The preliminary experiences, however, have been somewhat disappointing, especially if oral administration be used. These drugs are not without danger to the mother (thrombosis) or to the fœtus (paralytic ileus). In the treatment of *eclampsia* the use of 'veratrone' has recently again been advocated by Irving of Boston (1947), and for the control of the fits Dewar and Morris (1947) have had success with the administration of avertin rectally. More recently, intravenous pentothal has been used. Cæsarean section has only a limited place in the treatment of the toxæmia patient, but on occasions it is useful if the toxæmia be of acute onset and the child viable, and especially if there is some associated complication which renders Cæsarean section desirable. Failure to obtain clinical improvement with conservative measures may demand induction of labour by artificial rupture of the membranes.

THE RH FACTOR IN OBSTETRICS

The problem of the iso-immunization of an Rh-negative mother by an Rh-positive husband, with resulting hydrops fœtalis, icterus gravis neonatorum (with or without kernicterus) or congenital hæmolytic anæmia, is not so simple as was formerly envisaged. To date, there is no known method of adsorbing antibodies present in the mother's blood. It appears that little advantage is gained by the fœtus by premature induction of labour or by Cæsarean section before term, even in the presence of antibodies, and it would appear that the antibody titre is little guide to the degree of affection of the baby. It is estimated by Cappell (1946, 1947) that one marriage in eight and one pregnancy in ten involves the risk of iso-immunization, but that sensitization occurs in only one in 250.

The question of replacement transfusion *versus* small repeated transfusion ('topping up') of the fœtus affected with congenital hæmolytic anæmia is

still undecided. While the maternal antibodies pass freely into the mother's breast milk, there would appear to be no risk to the fœtus by breast feeding, as the antibodies are probably destroyed in the intestine of the fœtus.

EPISIOTOMY AND 'PROPHYLACTIC' LOW FORCEPS EXTRACTION

In America many obstetric units practise this routinely, but to date it has not found favour in Great Britain. There is in this country, however, a tendency to extend the use of episiotomy in order to diminish the incidence of subsequent genital relaxation and stress incontinence of urine. The success of the measure in these respects is dependent entirely upon the adequacy of the episiotomy repair. This must be done with full lithotomy position exposure and a careful layer by layer repair. The resulting perineum is soundly reconstituted, and when visiting the United States, I have been struck by the relatively small incidence of utero-vaginal prolapse in that country.

CÆSAREAN SECTION

Marshall (1949), in a recent survey of statistics of the large teaching units of this country, finds that the Cæsarean section rate is around 6 per cent. This increased incidence is undoubtedly due to the increased safety of the operation following the introduction of modern anæsthesia, chemotherapy and antibiotic therapy, the increasing employment of the lower segment operation, and the freer use of blood transfusion. Nowadays there are few indications for the classical (upper segment) operation. Even with placenta prævia the lower operation is advocated by many, and I endorse this view. The extra-peritoneal operations advocated by Waters and Norton in America, have never found favour in England. They were evolved too late, as the almost simultaneous advent of the antibiotics made them unnecessary.

ANÆSTHESIA

The perfect anæsthetic for obstetrical use has yet to be found. Local anæsthesia for Cæsarean section, whilst tedious and perhaps somewhat ineffective, can be a life saver—fœtal and maternal—in severely shocked or toxic patients. Local pudendal nerve block is excellent for episiotomy and breech extraction, and its use is increasing. Caudal analgesia is less popular in America than formerly. It has never been extensively practised here. Spinal anæsthesia has its advocates and its detractors, but impressive series have been published from time to time, and it would appear that success and safety depend upon the skill of the administrator and the choice of a non-toxic agent. Nitrous oxide and oxygen with a specialist administrator is probably the safest anæsthetic agent in obstetrics, although cyclopropane has its advocates.

For domiciliary use Minnitt's gas and air machine is safe and moderately effective, but its efficacy can be enhanced by the addition of the Chassar

Moir rebreathing bag attachment. Trilene is still under trial, as the perfect machine for domiciliary administration has yet to be evolved, and it is not yet certain that trilene is without some danger.

THROMBO-EMBOLIC DISEASE

The incidence of puerperal and postoperative thrombosis and embolism, for long a worry to the gynæcologist, has diminished as a result of early post-operative mobilization, together with early postoperative deep breathing, exercises, and massage. The percentage of fatal pulmonary emboli has been markedly reduced. The use of the anticoagulant, dicoumarol, has been discontinued because of its uncontrollable delayed action and its occasional effect on the liver cells. Heparin continues to be used with good effect both as a prophylactic and as a curative agent. The introduction of 'tromexan' by oral administration has afforded us an anticoagulant which appears to be safer than dicoumarol, in that its action is less prolonged and less delayed. All anticoagulant therapy must be controlled by repeated prothrombin estimations, and the aim should be to double the initial prothrombin time.

CANCER OF THE GENITAL TRACT

The earlier diagnosis of cancer of the female genital organs has been a feature of progress over the last five years, and this has resulted in the main from a keen appreciation on the part of both doctor and patient of the possible sinister significance of menstrual irregularities and post-menopausal hæmorrhage. The use of the vaginal and cervical smear techniques, together with the more frequent resort to exploratory curettage and biopsy, has enabled the diagnosis of corporeal and cervical cancer to be established in its earliest and curable stages. X-*ray* and *radium therapy* have become a relatively exact science, thanks to the help of the physicist, and it is now possible to administer adequate doses of radiation to the tumour site itself. Advances have been made towards the more accurate assessment of radio-resistance at a relatively early stage in radiation therapy, and this has encouraged an earlier surgical approach to those growths which appear to be resistant. For the more advanced uterine growths with extensive visceral involvement of the bladder or rectum, or both, *ultra-radical surgery* in the form of partial or complete pelvic exenteration is now possible. This ultra-radical surgery is on trial, but its justification is based on the findings that a relatively high proportion of patients dying from uterine cancer die with the disease still localized to the pelvis. It would appear obvious that before such operations are justifiable, careful clinical and X-ray examinations should so far as possible exclude the presence of distant metastases, especially in the lungs or bones. In like manner, carcinoma of the vulva is amenable to ultra-radical surgical attack as outlined by Stanley Way (1948, 1949). Malignant ovarian tumours, by their slow and insidious onset with little symptomatic evidence of their presence, continue to be diagnosed in their later

stages, but more frequent routine pelvic examinations are enabling the gynæcologist to diagnose more of these in their earlier and operable stages.

ARTIFICIAL MENOPAUSE

The use of X-rays and radium to induce an artificial menopause has been considerably restricted because of the frequent psychological upset caused to the patient, and because of the suggestion that such patients are subsequently rather more liable to the development of corporeal carcinoma. Endocrine therapy is useful in some of these as an alternative, but should this fail, as it often does, hysterectomy for functional uterine hæmorrhage is preferred to irradiation by most workers.

UTERO-VAGINAL PROLAPSE

The days of the pessary treatment of prolapse are ended except for those patients who refuse operative repair, or whose age or poor general condition contraindicates operation. The Manchester type of repair is well standardized and gives excellent results, although some authorities in dealing with patients over the age of forty prefer vaginal hysterectomy together with repair. An appreciation of the frequent association of enterocele, or hernia of the pouch of Douglas, with utero-vaginal descent, has led to increased care in the high posterior repair so necessary with the performance of most Manchester operations.

STRESS INCONTINENCE OF URINE

Over the past ten years dissatisfaction with the results obtained by minor suburethral operations in the treatment of this disabling condition has led to an appreciation of its importance, and has stimulated further efforts to effect a higher cure rate. The essential lesion would appear to be a descent of the bladder neck with rotation of the proximal urethra under the symphysis. No minor operation will effect a certain cure, and the operations devised by Kennedy (1937), and Treahy and Pacey (1948), have resulted in a cure rate of up to 90 per cent. by the vaginal approach alone. For the relatively small number of 'failed' cases by the vaginal route the various ingenious sling operations of Aldridge, Millin, Shaw and others offer more than a reasonable prospect of cure. It is rarely justifiable to perform a sling operation without at least one attempt at cure by the vaginal route, and a sling operation is never justifiable in the presence of utero-vaginal prolapse.

ENDOCRINOLOGY

The contribution of endocrinology to the treatment of gynæcological conditions is ever expanding. The abuse of endocrine therapy has been obvious to all, but recently this relatively young science has become more stabilized, thanks to the wisdom of its more sober exponents. Œstrogens have proved the most useful. Their effect in inhibiting lactation and ovulation are spec-

tacular, whilst their ability to ameliorate menopausal symptoms and to exert a beneficial effect on vulval and vaginal atrophic lesions is well recognized. Their use in amenorrhœa would seem to depend largely upon their ability to produce withdrawal bleeding. Progesterone appears to be of especial value in the treatment of *repeated abortion*, and recently, in such cases, progesterone pellets have been implanted deeply in the thigh to allow of even absorption. It is also used in the treatment of *metropathia hæmorrhagica*. The androgens seem to be especially effective in the treatment of *functional menorrhagia* and *involution mastitis*, and have proved beneficial in some cases of *endometriosis*. Endocrine therapy in the treatment of *infertility* has proved somewhat disappointing.

CONCLUSION

Such are a few of the more spectacular advances in treatment in obstetrics and gynæcology during recent years. Many more could be added if space allowed. These would include advances in pre- and post-operative care, the treatment of infertility, diabetes in pregnancy, the anæmias of pregnancy, and many others. Let it never be said that further advances are impossible. We are on the threshold of still greater achievement.

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ADVANCES IN PÆDIATRICS

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THIS is the thousandth issue of this journal and it is instructive to look back at the earliest numbers to see how pædiatrics was viewed in 1868. Dr. F. E. Anstie, one of the original editors, was physician to the Belgrave Hospital for Children, which was a guarantee that treatment of children's diseases would not be forgotten—and from that time onwards treatment has always been emphasized, for the subtitle of the original issues was 'A Monthly Journal of Therapeutics'. Of three remedies claimed to be of 'greatest value' for children—cod-liver oil, chloroform and iodide of potassium—today only for the first can it still be maintained that it has much use. Even this substance, however, has been supplanted, because the final conquest of rickets in Great Britain owes most to the addition of vitamin D to margarine (and hence an assurance of adequate intake for breast-feeding mothers) and to all dried milk for artificially fed infants. Of all the advances in the eighty years of *The Practitioner* the disappearance of rickets is perhaps one of the most striking.

Of other remedies mentioned in early editions many have been discarded. Physostigmine, described as 'promising' in the treatment of chorea (said to be uninfluenced by bromides), and glycerin of tannin for 'sponging out the pharynx' in 'hooping cough', which had not then acquired the 'w', have not survived. In fact, however, until quite recently, with the advent of the latest antibiotics on the one hand and the discovery of cortisone and ACTH on the other, the treatment of pertussis and chorea respectively has probably been no better than in 1868.

MORTALITY IN EARLY LIFE

Whatever may be the position of advances in the treatment of specific disorders, however, the general picture of child health today is remarkably better than in the last century. Professor Stanley Graham emphasized this point last year (Graham, 1950) in this journal and there is no need to repeat the figures then quoted. The infant mortality rate continues to drop in a most satisfactory fashion. Even the neonatal death rate is much lower than eighty years ago, although the drop has not been so steep for the first month of life as for the succeeding eleven months. The two main causes of death in the early days after birth are ***prematurity***, which is obvious and probably accurately reflected in official statistics, and ***infection***, which is more difficult to recognize and almost certainly underestimated.

Since the Ministry of Health, on the advice of its committee on the welfare of mothers and young children, inaugurated in 1944 a campaign to save more prematurely born babies (Ministry of Health Circular No. 20/44), the results have been most satisfactory. In London, for example, it is estimated that the neonatal mortality ascribed to premature birth has been halved in the past six years. The opening of special units in hospitals for the care of premature babies has undoubtedly played an important part, not only by a direct effect upon the survival of the very small infants, but also indirectly by training medical and nursing personnel for work in other hospitals and in the home. Domiciliary care of premature babies of 3½ lb. (1.5 kg.) or over, as Miller (1948) showed some time ago, can be just as effective as regards survival rates as hospital management. It is clear, however, that to get such good results the local health authorities must make available specially trained staff. Moreover, follow-up studies have shown that the small baby has only a slightly greater risk than the full-size newborn of suffering from physical or mental disadvantages in later life. A fuller discussion of this and other problems of neonatal care is contained in the valuable report of the Royal College of Obstetricians and Gynæcologists and the British Pædiatric Association (Ministry of Health, 1949).

One alarming exception to this general rule about the after-progress of premature babies must, however, be mentioned. This concerns the possibility of *blindness* in the smaller babies, due to retrolental fibroplasia. Terry, in 1942, first called attention to this apparently new problem when he reported the incidence of the condition as 1 per cent. in children under 3 lb. (1.3 kg.) at birth. Since that time even higher incidences have been reported. Minton and Cole (1951) quote Dr. Crosse as stating that in Birmingham retrolental fibroplasia occurs in 0.1 per cent. of all premature babies and in 4.2 per cent. of those under 3 lb. (1.3 kg.) at birth. Some American figures are alarmingly higher, but there seem to be almost violent fluctuations from year to year, and efforts are being made to determine the causative factors. The problem is undoubtedly serious, even if relatively small in relation to blindness as a whole. Moffat (1950) reports that out of 119 blind babies in the 'Sunshine Homes', twelve could be diagnosed as the result of retrolental fibroplasia. Whatever the cause it is possible that ACTH may prove valuable in treatment. Reese and Blodi (1951) have given 20 to 25 mg. of this substance daily to 14 babies diagnosed as suffering from the condition and report that the retrolental process has been arrested or has regressed in all cases.

NEONATAL INFECTION

Neonatal infection raises many fascinating problems of immunity, diagnosis and treatment. There is little doubt that faulty analogies with what happens in other animal species (with a different placental structure) have led to incorrect statements about antibodies in human colostrum. Equally there

is a popular misconception that newborn babies do not 'catch' infections, mainly because the passive immunity received from the mother to the common infectious fevers (if she possesses such immunity) does offer protection for a limited period. But immunity in the mothers to such recurrent infections as the common cold or staphylococci scarcely exists, and therefore babies can and do acquire such infections all too readily. Parish (1951) has recently reviewed this whole subject. The clinical picture of neonatal infection differs considerably from that in later life. Rises of temperature may be less (and the 'normal' temperature is lower to start with), the onset with vomiting may be mistaken for a feeding upset, cyanotic attacks are incorrectly labelled 'asphyxia neonatorum', and the development of œdema may produce a deceptively satisfactory gain in weight. A good working rule is to regard any disturbance in the new-born baby occurring after about the fifth or sixth day of life as due to infection until it can be proved otherwise. Detailed search should be made for evidence of an infected area—the upper respiratory tract, the umbilical stump, for example—and a blood culture made.

Treatment by penicillin and sulphonamide, the maintenance of breast feeding, and the use of a blood transfusion if anæmia develops, as it so often does, are the main lines of attack. Above all, expert nursing is essential, and because of this and the technical procedures involved in the treatment, hospital admission is essential in all but the mildest cases. Prevention would be a still better method of attack. Possibly one day means to increase maternal immunity antenatally may be devised. Meanwhile a scrupulous attention to personal hygiene on the part of those coming in contact with new-born babies is essential. The nose and the skin of the hands are the danger spots.

SULPHONAMIDES AND ANTIBIOTICS

Modern therapy has changed the whole outlook for the treatment of neonatal infection. It has also, of course, revolutionized the outlook for many other disorders of childhood. Nothing will be said about the *sulphonamides* except to emphasize that in the domiciliary treatment of children sufficient emphasis is not always laid upon the need for a really adequate fluid intake during the period of the administration of the drug chosen. Examples of anuria are occurring again with some of the more recent preparations, suggesting that more care is needed.

With the earlier *antibiotics* the main lines of recent progress have been concerned with improving means of administration and effectiveness. The value of *penicillin* given *by mouth* to small infants is clearly established, and in virtue of their low weight, and therefore the relatively small amounts of penicillin required, the cost of the drug involved is not excessive. Murray and Crawford (1951) suggest that for new-born infants, 100,000 units of procaine penicillin in aqueous suspension be given by injection twelve-

hourly for the first two days of treatment, followed, in the absence of any gastro-intestinal symptoms, by 100,000 units of sodium penicillin, four-hourly by mouth. With older children there is less certainty of action and the dosage is frankly extravagant. Doxiadis, Emery and Stewart (1951) have shown that to attain a reliable bacteriostatic level in the blood of children between two and fifteen years of age three hours after ingestion, a dose not smaller than 6000 units per lb. (13,200 units per kg.) body weight (i.e. 48,000 units per lb. [105,600 per kg.] in the twenty-four hours) is required, using penicillin in tablet form, each containing 200,000 units. The simultaneous administration of an antacid (sodium citrate, 3 g. in 1 fl. oz. [28.5 ml.] of flavoured water immediately before or after the penicillin) may allow a reduction in this dosage of approximately 50 per cent. But the penicillin must be given three-hourly round the clock, and this disadvantage and the fact that the dose required for mild infections by the parenteral route is only one-twelfth of that by mouth, are serious objections to the oral route for older children. The use of procaine penicillin in 2 per cent. aluminium monostearate, requiring an injection every twenty-four or even every forty-eight hours, as advocated also by the Sheffield workers (Emery *et al.*, 1949), would seem to be both more practical and more economical.

With *streptomycin* for tuberculous meningitis the search for improved results has concentrated upon means to prevent fibrinous adhesions, and thus a block to the free flow of cerebrospinal fluid with the threat of hydrocephalus, even in children who survive. Cathie (Cathie and McFarlane, 1950), continuing his use of streptococcal fibrinolysin or streptokinase to promote lysis of the fibrinous exudate, has obtained 23 survivors in a series of 40 patients, giving a figure of 58 per cent., which appeared to be the best in a table, given in his paper, including results from several centres. Honor Smith (Smith and Vollum, 1950), on the other hand, makes striking claims for the use of tuberculin intrathecally to provoke a local reaction which brings about a resolution of the fibrinous exudate. Further work is required to settle which of these two methods represents the better way to aid the action of streptomycin. Lorber (1951), in a recent controlled study with streptokinase (using a commercial preparation different from that used by Cathie), could not confirm the value of this substance in preventing blockage.

With *chloramphenicol* (chloromycetin) and *aureomycin* it is probably too early to be dogmatic as regards the diseases in children in Great Britain for which each is indicated, bearing in mind the supply position and the fact that strains of organisms (or possibly their drug resistance) may not be the same on both sides of the Atlantic. For infants and children, chloramphenicol may be given in doses of 100 mg. per kg. body weight per day, at four- or six-hourly intervals. It is not pleasant to take. Capsules are suitable for older children. For infants the bitter taste does not always cause trouble, but for them or for the difficult toddler age an emulsion in lemon syrup may be found effective. In this country the drug has mainly been used in child-

hood for pertussis, gastro-enteritis and certain types of urinary infections. Virus pneumonia, which appears to be rare in childhood, responds well to chloramphenicol. In other parts of the world its value in various types of typhus is established. For acute laryngo-tracheo-bronchitis in infants the benefit of this drug as suggested by Moncrieff and Weller (1949) has been confirmed by others (Forfar, Keay and Thomson, 1951).

With regard to the treatment of *pertussis*, the general verdict from the literature is that chloramphenicol is beneficial but not always dramatic in its results. Gray (1950), however, in a trial with out-patient children in London, goes further than this. Using 100 mg. per kg. body weight, once daily at bedtime for five days, he claims that it reduces the 'cough count', i.e., the number of paroxysms, as compared with controls and also lessens the whooping and vomiting, and 'loosens' the cough. Gray also claims good results with aureomycin in a daily dose of 50 mg. per kg. four-hourly for five days, given in capsules or in a chocolate sugar powder, with 50 mg., in a level teaspoonful for smaller children. (This suggests a possible very large number of teaspoonsful at a time for, say, a child of a year old weighing 10 kg.) Bogdan (1951) has suggested the use of chloramphenicol for whooping contacts and reports some modification of the subsequent illness. He gives the equivalent of 10 mg. per lb. (22 mg. per kg.) body weight daily for five days, divided into five doses a day mixed with jam or milk. The most recent study from the United States (Hazen *et al.*, 1951) contrasts the use of penicillin, aureomycin, chloramphenicol and terramycin in 150 children with pertussis. The children who received penicillin appeared to obtain some slight benefit, which developed slowly, but in those receiving one of the other three substances there was a more rapid decrease in the frequency and severity of the paroxysmal cough. In some patients there was an exacerbation of cough after the treatment was stopped. The effects of each of these three antibiotics were similar in all respects, and the dosage in each case was 60 mg. per kg. daily for ten days.

For *gastro-enteritis*, conflicting claims have been made and, as always with this disorder—still baffling although less frequently a cause of death in recent years—the problem of whether or not any drug directly attacks bowel invaders or indirectly helps by dealing with parenteral infection is still largely unsettled. In some centres appreciable benefit was obtained in infants with the diarrhœa and vomiting syndrome by the use of chloramphenicol, and to a lesser extent with aureomycin. Other centres claim no clear-cut benefit from either drug. Magnusson and his colleagues (1950) in Stockholm report the treatment of eight infants with aureomycin in an epidemic associated with the finding of a special strain of *B. coli*—in addition to other usual measures. After only a few doses the specific organism could no longer be found in the stools and, parallel with this, improvement took place in the general clinical condition. It is understood that carefully controlled trials with both these drugs are now being conducted in Great

Britain by the Medical Research Council, and the results are awaited with interest.

Other uses for aureomycin include the treatment of infections by penicillin-resistant staphylococci and peritonitis due to the *Bacillus coli*. For that comparatively rare disorder 'fibrocystic disease of the pancreas', aureomycin may be of great value in a maintenance dose of only 25 to 50 mg. twice a day, to prevent the harmful recurrent infections of the chest which complicate the condition. It is, however, necessary to warn users of this substance that extensive thrush, occasionally fatal, has been found to develop in some infants after its use, and obviously great caution and discrimination are necessary.

CORTISONE AND ACTH

In this country these drugs are in an even less advanced stage of availability than those just mentioned. Trials are proceeding and early experiences suggest that here, too, the results of colleagues in the United States cannot always be repeated. In childhood the hopes held out for the treatment of the acute phase of rheumatic fever have been those which have caused greatest interest, obviously because of the chance that here was the answer to the prevention of rheumatic heart disease. The American literature on this subject is already almost unmanageable. Using cortisone in patients with acute rheumatic fever numerous authors report the rapid disappearance, often within four to five days, of fever, tachycardia and arthritis, with a restoration to normal of a raised erythrocyte sedimentation rate and of abnormal changes in electrocardiograms. X-ray examinations show also a remarkable change of large heart shadows back to almost normal shapes within a week or so. Such immediate results are certainly superior to those hitherto attained by other means. Similar effects have been achieved with ACTH, and side-effects with either substance do not usually prove troublesome. Detailed study of early papers on this subject, however, raises difficulties. In the first place the predominance of adolescents in many of the series suggests that the commoner type in Britain—of acute rheumatic fever in the early school-age groups—may be a different syndrome. This is further strengthened by the statement in some reports that the fever and arthritis had not yielded to the administration of salicylate. Whatever the fundamental value of this drug, most physicians in Great Britain would agree that if given round the clock in adequate dosage the symptomatic response is almost constant. More recent American papers have been more cautious. Effects on carditis appear to be less definite than those on the fever or polyarthritis. The phrase 'suppression of rheumatic activity' is used to indicate that possibly nothing more fundamental occurs. A good and typical summary of the position is that by McEwen *et al.* (1950). Meanwhile, here again, trials are proceeding at centres in Great Britain with the limited supplies available.

The use of cortisone and ACTH for other disorders in childhood (except

in the Still type of rheumatoid arthritis, in which similar effects as with adults are obtained) is still limited to a few relatively rare conditions or to the occasional case of something commoner. Thus, as already mentioned, ACTH has been used in retrolental fibroplasia. Children with dermatomyositis have been successfully treated (e.g. Schlesinger, 1951). Scleroderma has been reported as improving but relapsing when ACTH is stopped. A report from Canada (Kanee *et al.*, 1950) deals with the use of this drug in an infant aged fourteen months with eczema. The dose was 10 mg. six-hourly. A striking improvement was noted in forty-eight hours.

BIOCHEMISTRY AND PÆDIATRICS

These new hormone preparations necessitate careful laboratory control of the electrolytes and water balance of the body and it is being confirmed, as McCance and others have already shown with regard to the very young infant, that the metabolic processes in early life may differ from those of later childhood or in adults. The immaturity of the infant's kidney is in fact responsible for this, lacking the power of concentrating. A fascinating disorder which is possibly due to a temporary error in metabolism is *infantile renal acidosis* (Lightwood, Black and Payne, 1951).

The story begins some years ago when calcification of the kidney tubules was reported in infants dying with wasting and often a terminal infection. Studying this nephrocalcinosis back to its earlier manifestations it was found that the infants passed an almost persistently alkaline urine and had reduced bicarbonate and increased chloride in the blood. The condition could be explained by a leak of bicarbonate by an immature kidney, and certainly the administration of alkali by mouth in the form of citrate will restore the blood chemistry to normal. After holding this at normal, so to speak, for a period the alkali can apparently then be withdrawn in some instances without a relapse, suggesting that the temporary abnormality of renal function has corrected itself.

It is too early yet to be certain if nephrocalcinosis can be completely prevented. The clinical state is vague. The infant, after getting on all right, begins to vomit, fails to thrive, and loses weight with a marked anorexia. The clue to diagnosis is the alkalinity of the urine, and this finding should lead to a full investigation of the blood chemistry.

Nephrosis is still a baffling disorder, and although cortisone is being tried, results are conflicting. The symptomatic use of an ion-exchange resin has been attracting attention. (This appears to work in a similar manner to the action of the domestic water-softener.) Payne and Wilkinson (1951) have treated six children, in each case securing some reduction of œdema, but the biochemical changes produced appear to be not only complex but not devoid of danger.

Another problem with a biochemical interest is the etiology of *pink disease*. Workers in Adelaide (Cheek and Stace, 1950; Hicks, 1951) reported

a low blood sodium in children with this condition and remarkably rapid cure by the administration of salt by mouth with, in some instances, the use of deoxycortone acetate. This led to the hypothesis of partial adrenal insufficiency which has come in for some criticism. Meanwhile, in a few instances in Great Britain workers failed to find reduced blood sodium, and Williams and colleagues in Melbourne (1951) have reported no reduction in blood sodium in 27 infants with pink disease as compared with a similar number of normal infants. They likewise failed to confirm any significant effect by the use of salt in treatment. The matter must be considered unsettled at present. It is perhaps a warning that biochemistry in pædiatrics (as at all ages) requires considerable clinical experience for its correct interpretation. Certainly the advances in this aspect of medicine would have seemed incredible in 1868.

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ADVANCES IN CARDIOLOGY

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THE selection of topics most worthy of consideration in a brief survey of recent advances in cardiology is necessarily somewhat arbitrary and, for the purpose of the present article, the term 'recent' has been taken to mean therapeutic measures which have come into general use in Britain only since the war. To decide which of these measures merit the title of 'advances' is more difficult, for many methods of treatment employed at the moment will doubtless later be discarded, and it is only the lapse of time that will enable us to say which of them have won an established place in therapeutics. For this reason, and on account of the limitations of space, I have decided to deal with a few topics only, rather than attempt to give a more comprehensive survey of a wider field.

SUBACUTE BACTERIAL ENDOCARDITIS

In 1945 the Medical Research Council initiated an investigation into the treatment of subacute bacterial endocarditis with *penicillin*. The results obtained in the first 147 cases treated were summarized by Christie (1946). These early observations showed that the duration of treatment was even more important than the total quantity of penicillin given, but that over the same period of time large doses were more effective than smaller ones.

In 1947, Morgan Jones and his colleagues reported in greater detail the results obtained in the first 33 cases treated in Manchester, and in 1948 Bramwell added a further series of 17 cases treated in the same clinic. These preliminary observations led us to believe that a course of treatment consisting of 500,000 units of penicillin daily for twenty-eight days would generally suffice to control the infection. Further experience, however, derived both from our own work and from that in other centres, has compelled us to modify this view, and we now consider that, to prevent relapse, larger doses are necessary. Of 71 previously untreated cases (Cates and Christie, 1951) given 500,000 units of penicillin daily for twenty-eight days, 14 relapsed or died with the infection uncontrolled, whereas of 18 cases receiving 2,000,000 units daily for four or six weeks none relapsed or died infected.

In the earlier stages of this investigation, only cases with a positive blood culture were included in the series, because the diagnosis in those with a negative blood culture might have been open to question. More recently, cases in which the clinical picture appeared to justify a diagnosis of subacute bacterial endocarditis, although no organism was isolated, have been treated. In many of these the diagnosis was confirmed post-mortem and, in some, organisms were found in the vegetations on the heart valves. Patients with a negative culture appear to be more resistant to penicillin. In the Manchester series there were 8 in whom we failed to get a positive blood culture, and of these only 2 were cured. In 34 patients with negative cultures in Christie's combined series, 6 were cured. It is probable, however, that the

large number of failures was partly attributable to inadequate courses of treatment and partly to the high incidence of heart failure before beginning treatment with penicillin.

To sum up, the present position appears to be that cases of subacute bacterial endocarditis may be divided into three groups:—

(1) Those sensitive to penicillin (i.e. those in which the coefficient of resistance of the infecting organism is less than four times that of the standard Oxford staphylococcus). In these there is a good prospect of being able permanently to control the infection, and fortunately the great majority of cases fall in this group. In 85 per cent. of cases the resistance of the infecting organism to penicillin was not more than twice that of the Oxford staphylococcus, and in only 4 per cent. was it eight or more times as resistant.

(2) Those in which the infecting organism is more highly resistant to penicillin. In such cases, even though the infection may temporarily be controlled with very large doses of penicillin (i.e. ten million units or more per diem), relapse is probable.

(3) Those in which isolation of the organism is not achieved. Many of these cases appear to be highly resistant to penicillin.

Broadly speaking it is our experience that patients who fail to respond to two million units daily for six weeks are unlikely to be cured by larger doses, although clinically the infection may be temporarily controlled. Our conclusions from these observations are that all patients in whom the coefficient of resistance is less than 4 should be given two million units daily for at least four weeks; and that in those in whom the coefficient of resistance is 4 or over, or in whom repeated cultures prove negative, much larger doses may be required to control the infection.

Of the 408 patients with positive blood cultures, 14.5 per cent. died during treatment and another 27.4 per cent. died in the first six months after treatment. In subsequent years an average of only 4 per cent. of the survivors died per annum (Cates and Christie, 1951).

The most important factors in prognosis are the presence of heart failure, and the state of nutrition of the patient before beginning treatment with penicillin. Both of these are largely dependent upon the duration of infection. Hence the importance of early diagnosis.

Several workers have made preliminary observations on the treatment of *penicillin-resistant cases* of subacute bacterial endocarditis with a combination of penicillin and streptomycin. The newer antibiotics have also been used, but the number of patients treated hitherto is not sufficient to warrant any firm conclusions.

CARDIAC SURGERY

Improvements in operative technique, new methods of anæsthesia, and new preoperative and postoperative therapeutic measures have all contributed

to the remarkable progress of thoracic surgery in recent years. Operation on the heart and great vessels has now become a routine therapeutic procedure.

In the period under review, the treatment of congenital heart disease has attracted special attention. It is curious how interest in this field has waxed and waned from time to time. In 1858, Peacock gave an admirable account of pulmonary stenosis and certain other congenital lesions. Yet in Mackenzie's classical textbook 'Diseases of the Heart', published fifty years later, only a page and a quarter were devoted to 'congenital affections of the heart'. For many years 'congenital morbus cordis' was considered an adequate diagnosis, and it was not until the publication of Maude Abbott's Atlas in 1936 that interest was reawakened. The 1000 cases of congenital heart disease analysed therein form the basis of our present knowledge of the subject.

Of the congenital malformations of the heart and great vessels amenable to surgery three only will be considered in the present article—the patent ductus, coarctation of the aorta, and pulmonary stenosis.

Successful ligation of the *patent ductus* was first reported by Gross and Hubbard in 1939. So popular has this operation become that Craaford (1951) is now able to record a series of 282 cases on which he has operated. In 16 of these the patent ductus was complicated by a large right heart with pulmonary hypertension, and in this group there were 8 deaths; of the remaining 266 patients only two died.

Some cardiologists recommend operation in all cases of patent ductus, because this abnormality throws a strain on the heart which may eventually lead to heart failure, and also, by providing a suitable nidus for the *Streptococcus viridans*, it renders the patient susceptible to an infective endarteritis. Others are more conservative, and are unwilling to advise operation when the patient is free from symptoms and the heart is not enlarged. They point out that one cannot exclude the possibility of spontaneous closure of the ductus even in later life. Surgical closure of the ductus will generally suffice to control the infection when infective endarteritis develops, but in seriously ill patients a preliminary course of penicillin lessens the operative risk.

The decision whether or not to operate on *coarctation of the aorta* is more difficult, for this is a much more formidable operation. Nevertheless, Craaford (1951) reported recently that to date 24 of his patients were well and at work five years after operation, and 17 of them were symptom-free. In a series of 100 cases of coarctation reported by Gross (1950), nine were found on exploration to be unsuitable for further operation, and eleven died. Gross considers, however, that in future, with the improvements in technique which have since been introduced, the surgical mortality should not be more than 5 or 6 per cent. Of his 80 patients who survived, hypertension was completely relieved in 71.

Surgeons are agreed that, in this condition, the upper age limit for opera-

tion is thirty years, since in older subjects arteriosclerotic changes in the aortic wall render the apposition of the cut ends more difficult, whilst on purely medical grounds operation is less strongly indicated in older patients, since, in those who survive the hazards of the third decade, when men are most likely to undertake strenuous physical exertion and many women have their first confinement, the outlook is relatively more favourable. There are few conditions, however, in which prognosis is so uncertain. Congestive heart failure is the most common cause of death; before the days of penicillin, bacterial endarteritis was a dreaded complication; subdural hæmorrhage from rupture of a congenital intracranial aneurysm is not uncommon and sudden death from rupture of the aorta is an ever-present danger, especially in patients who are symptom-free and may be unaware of their precarious condition. It is not surprising that cases have been recorded in which this has occurred in the course of an athletic contest, for many of these patients are men of fine physique and accustomed to indulge in strenuous exercise. Similarly, I always advise delivery by Cæsarean section in women with coarctation, on account of the risk of rupture of the aorta during childbirth (Bramwell, 1947). In fact I now regard this as probably the only cardiac indication for Cæsarean section.

In about 70 per cent. of 'blue babies' who survive the first two years of life the anatomical lesion is *Fallot's tetralogy*, the essential feature of which is stenosis of the pulmonary orifice with an aorta that overrides the ventricular septum and so communicates with both ventricles. The pulmonary stenosis may be valvular or 'infundibular' (i.e. situated at some distance from the valves, with a chamber of variable size intervening between the point of stenosis and the valvular orifice).

Cyanosis in this condition is due partly to mixing of the arterial and venous blood and partly to inadequate oxygenation of the blood, from defective blood supply to the lungs. Hence the degree of cyanosis is not necessarily proportional to the disability, nor is the improvement in the disability, following operation, always associated with a corresponding improvement in the patient's colour, although the two are commonly related. It is especially in dealing with the cyanotic type of congenital heart disease that team work, including both the physician and the radiologist, is so essential, for an accurate anatomical diagnosis is a prerequisite to successful operation. Fallot's tetralogy and other cyanotic types of congenital heart disease, such as tricuspid atresia, which are amenable to surgical treatment must be distinguished from conditions such as the Eisenmenger complex, in which the pulmonary artery is dilated and the lungs well supplied with blood, and in which a systemic-pulmonary anastomosis would serve no useful purpose. X-ray screening will generally enable the physician to determine whether or not the blood supply to the lungs is defective, but in some cases special methods of investigation, such as angiocardiography and cardiac catheterization, may be necessary. I am, however, in complete

agreement with Sellors and Bolcher (1950) in considering that angiocardiography and cardiac catheterization should be employed only in cases in which the diagnosis is in doubt and difficult to establish, since neither of these methods is free from risk, and many patients assert that the former is an extremely unpleasant experience.

In the *Blalock-Taussig operation* the pulmonary artery is anastomosed to the innominate or to one or other subclavian artery, whilst in Pott's operation, which serves a similar purpose, the anastomosis is between the pulmonary artery and the aorta. In about 70 per cent. of cases the therapeutic result of these operations is dramatic; not only is there an almost miraculous improvement in the exercise tolerance, but the rapid bodily and mental development of the child is remarkable.

At the International Congress of Cardiology in Paris in September 1950, Helen Taussig reported that the operative mortality in 716 cases of Fallot's tetralogy operated on by Blalock and his colleagues was 19 per cent. That this risk is worth running seems clear from Campbell's analysis (1950) of 340 such cases not treated surgically. He found that 1 patient in 2 died before the age of seven, 3 out of 4 died before the age of fourteen, and 9 out of 10 before the age of twenty-one.

Sufficient time has not yet elapsed to allow of assessment of the ultimate prognosis in these cases, nor to say how well the heart will tolerate the additional strain thrown upon it by the artificial ductus; but, as a life-saving measure, the immediate result is remarkable.

An alternative method of treatment in this condition is to enlarge the stenosed pulmonary orifice by *valvulotomy*. Brock and Campbell (1950) have reported a series of 33 cases, 18 of which had pure pulmonary stenosis and 15 Fallot's tetralogy, treated by this operation. There were 10 deaths in this series, mostly among older patients. Of the 23 survivors the result in 18 was quite comparable with that obtained by the Blalock-Taussig operation. These workers are of opinion that valvulotomy is the operation of choice in cases of pure pulmonary stenosis; but whether direct operation will prove equally successful in Fallot's tetralogy, especially when the stenosis is infundibular, is more doubtful. Preferably, valvulotomy should be undertaken before the age of ten if the best results are to be obtained. In patients over twenty the surgical risk is much greater. The same applies to systemic-pulmonary anastomosis.

The success of valvulotomy in pulmonary stenosis naturally suggested a similar line of attack on *mitral stenosis*. This operation had been performed many years ago by Cutler in Boston and by Souttar in London, but the high mortality under conditions prevailing at that time led to its abandonment. Great as is the popular appeal for the relief of congenital heart disease, new and effective methods for the treatment of rheumatic heart disease are clearly much more important, the incidence of rheumatic heart disease being more than ten times that of congenital heart disease. Now, thanks to improvements in anæsthesia, antibiotics, anticoagulants and other pre- and post-operative measures, this operation has become a reasonable sur-

gical risk and, at a recent meeting of the Royal Society of Medicine, Brock (1951) reported 48 valvulotomies for mitral stenosis with only 8 deaths. Unlike congenital heart disease such as Fallot's tetralogy, or the patent ductus, in which the best results are obtained in children, patients with mitral stenosis under twenty years of age are, at present, generally regarded as unsuitable for operation on account of their greater liability to active rheumatic infection. Brock does not regard either auricular fibrillation or embolism as a contraindication to operation, although obviously patients with long-standing congestive heart failure are unsuitable.

ANTICOAGULANTS IN CORONARY THROMBOSIS

There is no doubt that the mortality in coronary occlusion can be considerably reduced by the use of anticoagulants. In a series of cases recently published by Tulloch and Gilchrist (1950), it was 23 per cent. in cases so treated as compared with 41 per cent. in a control series. There is, however, still some difference of opinion regarding the type of case in which these drugs should be used. As Tulloch and Gilchrist point out, an important consideration in prognosis is the functional efficiency of the heart prior to infarction. If cases are graded in accordance with their disability, those in Grade I (i.e. patients who are asymptomatic) usually recover, provided they survive the initial period of shock, whilst those in Grade IV (who have symptoms of heart failure at rest) always die. The great majority of cases, however, fall in Grade II (the functional capacity of the heart being only slightly impaired before infarction). It is in this group that the use of anticoagulants is most likely to turn the scale. Nevertheless, these writers consider that anticoagulant therapy merits consideration in all cases of myocardial infarction.

Papp and Shirley Smith (1951) have approached the problem from rather a different angle. They classify their series of 200 cases of cardiac infarction in three groups—70 slight, 42 moderate, and 88 severe. Slight cases they define as those in which shock and heart failure are absent, in these they believe that the infarction is subepicardial and rarely reaches the endocardial surface. Severe cases are those exhibiting persistent shock and early congestive heart failure. It is in the latter only that they consider anticoagulant treatment necessary.

When this method of treatment was first introduced, the usual procedure was to give dicoumarol by mouth and, during the first forty-eight hours, to supplement this with intravenous heparin. Dicoumarol is a dangerous drug and the dosage necessary to produce the desired effect—a prothrombin concentration in the neighbourhood of 20 per cent.—varies widely in different patients. It is essential to control treatment by repeated prothrombin estimations; for, if the prothrombin concentration falls below 20 per cent., serious or even fatal hæmorrhage may occur. This consideration unfortunately renders the drug unsuitable for domiciliary use.

Most cardiologists now regard 'tromexan' as preferable to dicoumarol in that it induces hypoprothrombinæmia more rapidly and, being more rapidly destroyed and excreted, is less likely to cause prolonged hæmorrhage.

Professor R. B. Hunter has kindly allowed me to refer to a hitherto unpublished clinical investigation on tromexan carried out in his department. In a series of 111 cases treated with this drug for various thrombotic episodes, including deep venous thrombosis of the veins of the calf, pulmonary embolism and coronary thrombosis, the incidence of thrombo-embolic complications was only 4.5 per cent. This remarkably low figure is attributed to keeping the prothrombin level in the neighbourhood of 20 per cent. It was found that this level could be induced by tromexan in 78 per cent. of cases in forty-eight hours, a shorter time than is required to produce a similar result with dicoumarol. As in the case of dicoumarol, laboratory control is essential, since the dose required for induction varies considerably in different patients, as does the maintenance dose, the average figures being 1,200 mg. per day and 600 mg. per day, respectively. Administration in divided dosage was found to be more effective than a single dose. On discontinuing the drug the prothrombin level reached 30 per cent. (above which level there is little danger of hæmorrhage) in twelve hours in the case of tromexan, whereas it took much longer to do so in the case of dicoumarol.

HEART DISEASE IN PREGNANCY

Recent additions to knowledge of the physiology of the circulation in pregnancy have modified considerably our attitude to the dangers of pregnancy in patients with heart disease. It was customary to believe that the strain on the heart increased steadily as pregnancy advanced and, on this account, the induction of premature labour or Cæsarean section was sometimes advised in women with heart disease, in order to avoid the strain of the final month of pregnancy. We now know that the blood volume and cardiac output increase up to about the 32nd week, but thereafter diminish, and that the strain on the heart is correspondingly decreased. Clinically this accounts for the fact that the incidence of heart failure progressively increases up to the 32nd week and then diminishes (fig. 1). We now believe therefore that there is no cardiac indication for the induction of premature labour or for Cæsarean section, with the possible exception of coarctation of the aorta.

Morgan Jones (1951), to whom I am indebted for figure 1, has recently reported his observations in 485 cases of organic heart disease complicating pregnancy seen during the last few years, and it is gratifying to find that the mortality is considerably less than in a similar series of 350 cases, from the same clinic, reported by Bramwell and Longson in 1938. This improvement appears, at any rate partly, to be attributable to the fact that, as experience has increased, we have become more and more reluctant to interfere with the normal course of pregnancy. We now believe that when there is no obstetric indication for operative interference, delivery by natural forces imposes less strain on the heart than Cæsarean section and that pregnancy should be allowed to pursue its normal course. Admittedly, this is a negative attitude but, from the patient's point of view, it is a no

less important advance in therapy than that achieved by the use of some new drug.

The chief lesson we learnt from our earlier series of cases was the importance of adequate antenatal supervision. The mortality among patients

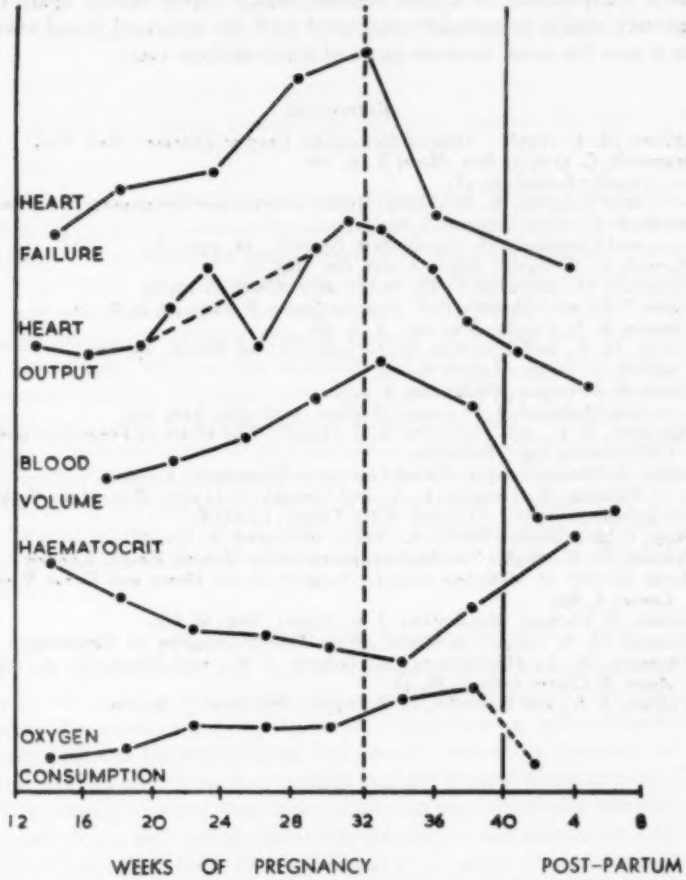

FIG. 1.—To illustrate relation of cardiac output and blood volume to incidence of heart failure. The curves are taken from the work of the following authors: heart failure—Hamilton and Thomson (1942); heart output and oxygen consumption—Burwell (1938); blood volume—Thomson, Hirscheimer, Gibson and Evans (1938); hæmatocrit reading—Cohen and Thomson (1936). Reproduced by kind permission of Dr. A. Morgan Jones and Messrs. Harvey and Blythe, Ltd. from 'Heart Disease in Pregnancy'.

admitted to hospital as 'urgencies' with congestive heart failure was sixteen times as great as that among patients who had been under supervision

throughout pregnancy and, provided adequate antenatal care is established, congestive heart failure need no longer be regarded as a serious complication, for, if recognized early, it generally responds well to treatment. Sudden left heart failure with acute pulmonary œdema is much more alarming. It is a complication of mitral stenosis which rarely occurs apart from pregnancy, and is presumably associated with the increased blood volume. This is now the most common cause of death in these cases.

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ADVANCES IN THE TREATMENT OF BLOOD DISEASES

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Since the senior author last reviewed this subject in *The Practitioner* of October 1947, many noteworthy advances have marked the progress of knowledge and treatment in hæmatology. A further four years of experience with drugs which were comparatively new and untried at that time, such as folic acid, urethane, and nitrogen mustard, have made possible a more balanced assessment of their value in therapy. Important new discoveries have been made, such as the isolation of vitamin B_{12}, folinic acid, the adrenocorticotrophic hormone, cortisone, and the folic acid antagonists; all of which have proved of great interest in the study and treatment of blood diseases. The introduction of preparations of iron for intravenous injection has provided a valuable new measure in the therapy of selected cases of iron-deficiency anæmia. The purpose of this article is to summarize for the busy general practitioner the significance of such advances, and to comment on the current status of new remedies in the light of present knowledge and experience.

FOLIC ACID, VITAMIN B_{12}, AND FOLINIC ACID

In 1947 it appeared that *folic acid*, which had been synthesized by Angier in 1945, was probably the specific anti-anæmic factor required for the continuation of normoblastic blood formation. Since then the whole question of the maturation of the erythroblast has become even more complex, as the result of the isolation in 1948 of vitamin B_{12}, and in 1950 of folinic acid. The interrelationship between these three factors has yet to be finally determined.

Vitamin B_{12}, a red, cobalt-containing substance, was isolated in 1948 in crystalline form from fresh liver by Rickes *et al.* in the United States, and simultaneously by Lester Smith in Great Britain. It has since been made commercially from the mould which produces streptomycin, and is now freely marketed at a price which compares favourably with that of liver extracts. Extensive clinical trials of vitamin B_{12} have shown that this substance is at least as effective as purified liver extracts in the initial therapy of Addisonian pernicious anæmia, and for the prevention and treatment of subacute combined degeneration of the spinal cord. Although it will require several years before a final assessment can be made of its value in the main-

tenance treatment of such patients, the evidence at present available suggests that it is also satisfactory for this purpose. Another advantage of vitamin B_{12} is that it is a crystalline substance containing no foreign protein. Accordingly it is non-antigenic, so that sensitivity reactions, which sometimes occur with liver preparations, are not encountered.

The initial dosage of vitamin B_{12} recommended for untreated cases of pernicious anæmia is 50 micrograms given intramuscularly, and repeated at weekly intervals until a normal blood picture is restored. Thereafter, maintenance requirements vary with individual cases, but the consensus of opinion seems to be that at least 50 micrograms should be injected every three weeks. Ungley (1949) has studied the optimum dosage in patients with subacute combined degeneration and recommends that in them the weekly dosage of 50 micrograms should be continued for six months with half this amount thereafter. At the least sign of relapse, or if intercurrent infection occurs, the dosage should again be increased.

Vitamin B_{12} therapy has been found to be completely or partially ineffective in the treatment of the megaloblastic anæmias associated with pregnancy, infancy, malnutrition, and the malabsorption syndrome. Liver extract is also often ineffective in these anæmias, in which *folic acid* is the drug of choice and can be used with safety as there is little or no danger of subacute combined degeneration in such patients. Up to the time of writing it is doubtful if there has been an authentic case of megaloblastic anæmia in which folic acid has failed to restore normoblastic blood formation. It has, however, been found that some cases of Addisonian pernicious anæmia fail to maintain a satisfactory blood level, despite continued maintenance treatment with folic acid.

Folinic acid, or the citrovorum factor, is a recently discovered substance which is chemically related to folic acid, and is necessary for the growth of a streptococcus named *Leuconostoc citrovorum*. The therapeutic applications of this factor are still being investigated, and it is so far not available commercially. It has been shown, however, to be effective in the treatment of Addisonian pernicious anæmia (Davidson and Girdwood, 1951). The same authors have had an excellent response in a patient with the megaloblastic anæmia of pregnancy.

The exact interrelationships of folic acid, vitamin B_{12}, and folinic acid are of considerable academic interest and have been the subject of much debate and research, including the time-consuming and intricate techniques of microbiological assay and chromatography. The activity of concentrated liver extracts appears to depend essentially upon their content of vitamin B_{12}, since folic acid and folinic acid are only present in very minute quantities. Castle, who did so much of the basic work on the etiology of pernicious anæmia, has produced evidence that vitamin B_{12} constitutes the 'extrinsic factor' originally propounded in his hypothesis. It is now believed that the function of the 'intrinsic factor' of the stomach is to promote the absorption of the vitamin from the alimentary tract. Strong support is given to this view

by the fact that vitamin B_{12} does not produce any hæmatological response when administered orally to patients with pernicious anæmia, in amounts that are effective when administered parenterally, unless normal gastric juice is given at the same time. It is probable that vitamin B_{12}, folic acid and folinic acid all play some essential but little understood rôle in the metabolism of nucleic acid, and that all three factors are required for the continuation of normoblastic blood formation. Until these academic questions are answered by further research it is sufficient to reiterate here that for practical clinical purposes, liver extract and vitamin B_{12} are the drugs of proved value for the treatment of Addisonian pernicious anæmia, whilst folic acid remains the therapeutic agent of choice in the much rarer megaloblastic anæmias associated with pregnancy, malnutrition and malabsorption. Folic acid should not be used for the treatment of Addisonian pernicious anæmia, because of its inability to prevent the development of subacute combined degeneration of the spinal cord.

INTRAVENOUS IRON THERAPY

All clinicians are familiar with patients who present with the manifestations of chronic iron-deficiency anæmia and who either cannot or will not take iron by mouth because of the gastro-intestinal symptoms which follow. In most instances the difficulty can be overcome by one or more of the following procedures: (1) by starting treatment with a small dose of oral iron and gradually increasing it until the optimal dose is reached; (2) by insisting that the iron is taken only after meals; (3) by trying preparations of iron other than the one causing the symptoms. However, in some individuals genuine intolerance to oral iron undoubtedly occurs. Again, in other patients intensive oral therapy fails to correct a *microcytic hypochromic anæmia*, due presumably to some defect in the absorption of iron. For these reasons there has for long existed a need for a satisfactory preparation of iron suitable for parenteral administration, but repeated attempts to introduce such a preparation had failed because of the difficulty in producing therapeutic effects without simultaneously inducing severe toxic reactions. In 1947, Nissim described satisfactory results with a preparation of saccharated iron oxide, and since then sufficient clinical trials of intravenous iron therapy have been reported to allow an assessment of the value of such treatment.

'Ferrivenin' (Benger) and 'iviron' (British Schering) are proprietary preparations of saccharated oxide of iron which can be administered intravenously with little risk of untoward reactions; 100 mg. of elemental iron are contained in solution in a 5 ml. ampoule, so that the injection of this dose should provide enough iron to raise the hæmoglobin level by approximately 4 per cent. It is usual to give 40 mg. as the first injection, and thereafter 100 mg., or 200 mg. at the most, every second or third day until a satisfactory hæmoglobin level is reached. Reactions such as nausea and backache associated with a degree of circulatory shock are infrequent, but are sufficiently severe to render the treatment unsuitable for use in general practice, unless

the practitioner is prepared to keep the patient under observation for an hour or so after each injection. Although it is impossible to predict which patients will exhibit toxic reactions, there is good reason to believe that the latter are less likely to happen if the material is injected slowly and in amounts not exceeding 200 mg. of iron at any one injection. It is also important to remember that the total dosage of iron administered in a course of injections should not exceed 1.0 to 1.5 g., and, as there is a high retention of the injected metal in the tissues, courses should not be repeated for at least two to three months.

The iron-deficiency anæmias associated with the *malabsorption syndrome* in children and adults (e.g. cœliac disease, idiopathic steatorrhœa, tropical sprue and intestinal hurry due to short-circuiting operations or inflammatory diseases of the intestinal tract) are often refractory to oral iron therapy and can usually be greatly helped by intravenous therapy. Sinclair and Duthie (1950) have reported considerable improvement in the hæmoglobin levels of anæmic patients with rheumatoid arthritis who were refractory to oral iron. They suggest that in this disease there exists a marked increase in the needs of the tissues for iron. Good results have also been obtained in patients who have been proved genuinely intolerant to oral iron therapy, and also in certain anæmic cases in which, for unexplained reasons, adequate and prolonged oral treatment has failed to produce the expected rise in hæmoglobin. Intravenous iron therapy has undoubtedly proved a valuable advance in hæmatological treatment, but it must be emphasized again that the indications for it are strictly limited, and it should be employed only in selected cases after a thorough trial of oral iron medication.

URETHANE

This simple compound was introduced by Haddow and his co-workers in 1946 for the treatment of leukæmia, and in the first report of its clinical trial by Paterson *et al.* (1946), satisfactory responses were obtained in cases of *chronic myeloid leukæmia*. During the past five years it has been shown that urethane is of no value in the therapy of acute leukæmia or in reticulosis of the Hodgkin's group, and is far inferior to X-rays in chronic lymphatic leukæmia. It undoubtedly produces an effect in most cases of chronic myeloid leukæmia, but on the whole the results are no better, and often not so good, as those obtained by radiotherapy. Many patients complain of extreme nausea caused by the drug, and reduction in the size of the spleen is rarely so complete as with X-rays. In this country where most patients are within easy travelling distance of centres of radiotherapy, courses of irradiation are the treatment of choice for chronic leukæmia. Urethane therapy may be considered in remote areas, and has been used to prolong the remissions induced by X-rays in the chronic myeloid variety.

Some workers have reported favourably on the effects of urethane in *multiple myelomatosis*, claiming relief of bone pain, and a reduction in the abnormal plasma proteins as indications of improvement. Whilst irradiation

remains the treatment of choice in this disorder, urethane is a drug which is worth a trial when X-ray therapy has failed to relieve the condition. Stilbamidine, which was recently recommended for the treatment of multiple myelomatosis, has been found not to change the course of the disease.

NITROGEN MUSTARD

The nitrogen mustard group of drugs owe their introduction to war-time research into the systemic toxic effects of mustard gas, which was found to produce severe depression of bone marrow function. In the last few years there have been several reports of the trial of methyl-*bis*(β-chloroethyl)-amine hydrochloride in the treatment of *reticulosis* and *leukæmia*, and we have had considerable experience in its use in these conditions.

On the whole, nitrogen mustard therapy has little to offer that cannot be better achieved by X-ray therapy. It is of no value in acute leukæmia, and is too toxic and uncertain to be recommended in the routine treatment of chronic leukæmia, in which X-rays are in general far more satisfactory. Its main value seems to lie in the palliative treatment of selected cases of generalized *Hodgkin's disease*, in which American authorities, such as Dameshek *et al.* (1949), consider it an indispensable drug. Whereas localized X-ray therapy remains the best treatment for early cases of lymphadenoma with involvement of one or more groups of superficial glands, many physicians can recall the pathetic picture of the terminal case when the condition has become widespread and further irradiation is contraindicated because of hypoplasia of the bone marrow and increasing radio-resistance of the tissues affected by the disease. Some of these terminal cases can be 'salvaged' for periods of several months by nitrogen mustard therapy. Again, there are cases which from the early stages have extensive visceral involvement associated with anæmia and constitutional symptoms. Remarkable remissions can sometimes be achieved in such cases. The type of case suitable for this treatment requires careful selection after joint consultation between an experienced radiotherapist and the hæmatologist, since both nitrogen mustard and irradiation may be used advantageously in a planned course of treatment.

The recommended dosage of nitrogen mustard is 0.1 mg. per kg. of body weight, administered on successive or alternate days, with a total of three to six injections. The usual initial amount is 4 to 5 mg., and if this is well tolerated, succeeding doses can be increased, although not more than 8 mg. should be given at one injection. The best technique for administration is to inject the required amount of a freshly prepared solution of the drug into the rubber tubing of a freely running saline intravenous infusion. Severe local reactions and thrombosis may result from extravasation of nitrogen mustard outside the vein. In the majority of patients, generalized toxic reactions occur within a few hours of an injection and last for a further hour or so. Rigors and vomiting are frequent among such early effects, but it must be remembered that profound leucopenia and thrombocytopenia can

also result and necessitate suspension of treatment. Courses of intravenous nitrogen mustard should not be given at intervals of less than six to eight weeks. Clinical trials of nitrogen mustard preparations which can be administered by mouth are now in progress. These oral preparations have only been employed in certain selected centres, and further research and observations are necessary to establish their therapeutic value. There are indications, however, that they may be of value in certain carefully chosen cases of reticulosis and chronic lymphatic leukæmia.

FOLIC ACID ANTAGONISTS

In 1948, Farber and his co-workers observed what they described as an 'acceleration phenomenon' in the rate of progress of acute leukæmia in children who were given folic acid. They therefore decided to try in the treatment of this disease, chemical analogues of folic acid which had been found to exert an antagonistic effect on the growth-promoting properties of folic acid on certain organisms. *Aminopterin*, or 4-aminopteroylglutamic acid, was shown to be the most potent biological antagonist to folic acid. In humans it is a most dangerously toxic drug, producing profound hæmatopoietic depression, and ulceration in the alimentary tract.

In the last three years the clinical trial of aminopterin in cases of acute leukæmia has been limited to a few research centres, as the drug is far too toxic for general release. Farber (1949) and Dameshek *et al.* (1950) have reported on about 100 cases, and one of us (Innes, 1949, 1951, and unpublished work) has treated nearly 40 patients in Edinburgh. In general the results have been disappointing, although aminopterin is the first drug that has been proved capable of influencing the course of this disease, and as such is of profound interest and importance for future research. The most striking effects have been found in children with the acute form of lymphatic leukæmia. In approximately one-third of such cases treatment has induced remarkable clinical and hæmatological remissions lasting for several weeks, and in a few cases has prolonged life for periods of up to nearly two years. It is not, however, a cure, as relapse and a fatal termination are inevitable. Adults and children with other types of acute leukæmia show little response. In general, remissions are short-lived, and the drug often causes such severe toxic effects that the consensus of opinion is that its use cannot be recommended for the routine treatment of acute leukæmia. It is to be hoped that the search for similar, but less toxic compounds, will prove more successful in the near future.

ADRENOCORTICOTROPHIC HORMONE AND CORTISONE

It is only possible at present to comment briefly on the use of ACTH and cortisone in the treatment of blood diseases, as this subject is still very much in the research stage and more time will be required before a balanced assessment of their therapeutic value can be made. When it was found that these hormones could induce a regression in the lymphoid tissues of the

body, it was hoped that they would prove of value in the treatment of leukæmia in general, and lymphatic leukæmia and certain related reticuloses in particular. In a proportion of cases of acute leukæmia, especially of the lymphatic type, dramatic remissions have been reported, in some of which both the peripheral blood and bone marrow have appeared to return to normal. Unfortunately, such remissions have lasted only a few weeks or months and death has occurred in every case despite continued hormonal treatment. The results obtained in the chronic types of leukæmia and in the reticuloses have been even less satisfactory.

It is also sad to relate that the encouraging results reported in the treatment of idiopathic thrombocytopenic purpura and acquired hæmolytic anæmia with cortisone and ACTH must be accepted with caution, since many cases of these diseases have failed to show improvement. Likewise, poor results have been obtained in aplastic anæmia, myelosclerosis, multiple myelomatosis, and congenital acholuric jaundice. The failure to repeat the highly promising results first reported in certain blood diseases has been a grave disappointment to hæmatologists.

SPLENECTOMY

Splenectomy has long been recognized as the treatment of choice for certain blood diseases, such as congenital acholuric jaundice and idiopathic thrombocytopenic purpura. In the last few years more and more hæmatologists have come to accept the view that an overactive spleen may produce a factor which inhibits the production by the bone marrow of the formed elements of the blood. Such hæmatopoietic depression is thus held to be the result of ' hypersplenism'. This condition may develop idiopathically or in association with recognized causes of splenic enlargement. Splenectomy should be considered in all such cases if they fail to respond to a thorough trial of orthodox medical treatment.

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ADVANCES IN NEUROLOGY

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During the past quarter of a century notable advances have been made in the treatment of diseases of the nervous system. With modern chemotherapy and good nursing the death rate from meningococcal meningitis has fallen from over 20 per cent. to under 5 per cent., whilst recovery from other forms of pyogenic meningitis is now the rule rather than the exception. To the growing list of diseases controllable by antibiotics can now be added tuberculous meningitis. Many myasthenic patients can be relieved by prostigmin or thymectomy to a degree which was not formerly possible. Improved surgical and neuro-radiological techniques have advanced the treatment of congenital abnormalities of the cerebral blood vessels, and have made the outlook for a patient with a brain tumour more favourable. In order that such patients may derive the maximum benefit from treatment it is essential that they should reach the neurosurgeon at a stage when operation is likely to have the maximum chance of success. Therefore the general practitioner must be able to recognize not only the early symptoms of cerebral tumour, but also those due to hæmorrhage into the subarachnoid space ('leaking' aneurysm) and into the extradural and subdural spaces (extradural and subdural hæmatoma). These types of cerebral hæmorrhage constitute emergencies, since a delay of a few hours may gravely prejudice their chances of survival.

Further advances in medical treatment will come with the growing appreciation of the fact that the primary cause of certain neurological diseases may be sought in the field of general medicine.

POLIOMYELITIS VIRUS INFECTION

There is no known medical agent which will inhibit the action of the viruses of poliomyelitis. Therefore all that can be done is to reduce so far as possible the risk of paralysis, first by recognizing early symptoms, and secondly by avoiding those factors which may facilitate the passage of the virus from the throat and intestine, or decrease the resistance of the motor nuclei in the brain-stem and spinal cord.

During an epidemic, many minor illnesses, especially in children, are caused by the virus. Less often these minor complaints are accompanied by severe headache and changes in the cerebrospinal fluid (non-paralytic form). Factors which may determine the onset of paralysis include: (1) recent tonsillectomy; (2) recent inoculation, especially in children; (3) infections of the throat and intestine; (4) physical fatigue. The first two are avoidable. During an epidemic, patients with tonsillitis and gastro-enteritis

should remain at home and receive treatment with appropriate sulphonamide drugs. Return to school or work should be deferred until recovery is quite complete. Lastly, the effect of physical fatigue can be partially mitigated if the general practitioner will order to bed without delay any patient, who, during the summer and autumn months, presents with fever, malaise, headache, pains in the back or limbs or increased sensitivity of the skin. During an epidemic parents may be reassured about the small risk of paralysis (roughly 1 in every 100 infected by the virus), and the importance of rest in bed if their child develops any minor illness.

Although poliomyelitis virus is at the present time the most common cause of meningitis in this country, if the non-paralytic form is suspected, an examination of the cerebrospinal fluid should be made in order to confirm the diagnosis and at the same time exclude infection by pyogenic organisms or the tubercle bacillus. It will be generally accepted that paralytic cases of poliomyelitis should be admitted to hospital in order that the maximum benefit may be obtained from skilled nursing and aftercare. However, during a large epidemic the general practitioner may be called upon to treat the milder type of case at home.

Treatment of the Mildly Paralytic Poliomyelitis Case at Home

Precautions should be taken against further spread within the household, although it is likely that other members of the family will also be harbouring the virus. Masks should be worn by those entering the sick room for a period of five days after the fever has subsided. The hands should be washed in an antiseptic solution immediately after leaving the sick room. Excreta need not be carbolized unless sanitary conditions are primitive.

Treatment should have two objects, first to limit so far as possible the spread of paralysis, and secondly, to ensure the maximum degree of recovery. The first object will be attained if the practitioner impresses upon relatives and the patient the necessity of complete rest in bed; in practice this means that the patient is not allowed to get out of bed for toilet purposes. Changes of position may be allowed. The period of absolute rest covers the pyrexial phase and for a week or ten days afterwards. Initially, a quick but thorough examination should be made of all muscle groups, not omitting those controlling the neck, abdomen, the back and proximal joints of the limbs. A note should be made of the degree of loss of power. No further examination should be necessary until fever has subsided, when a fresh assessment of paralysis should be made.

The diet should be light, and fluid should be given freely. Analgesics may be necessary to allay restlessness consequent upon pain or spasm. If the patient is anxious, phenobarbitone in adequate doses should be given. If spasm is a marked feature, a trial may be made of drugs which paralyse the sympathetic, such as 'priscol' (25 mg. two or three times daily).

In order to achieve maximum recovery, the affected limbs should be placed so that the paresed muscles are not stretched; this position can be

maintained by a firm pillow or padded sandbag. After the first week passive movements at all joints in the affected limb should be carried out by a nurse or relative.

Physiotherapy.—Provided pain and spasm have largely subsided, active treatment may begin two or three weeks after the termination of fever. The services of a well-trained physiotherapist are invaluable in securing the intelligent cooperation of the patient. Exercises are graded according to the degree of paresis; if this is marked, movements must be assisted. The elimination of gravity is an important aid in the treatment of the paralysed limb; this can be achieved either by the use of slings (Guthrie-Smith apparatus, of which there is a form suitable for use in the home) or by means of exercises in a bath. The average case of mild paralysis should not be kept in bed for longer than three weeks. Since the type of case under discussion is a relatively mild one, it will be assumed that considerable improvement will have occurred by the end of a month. The patient and the relatives should be told that daily exercises under the supervision of a physiotherapist will be necessary for a further period of one to six months, depending upon the degree of paresis and the rate of improvement.

DISSEMINATED SCLEROSIS

Disseminated sclerosis is regarded by the average consultant and general practitioner as a disease which runs a variable but inexorable course towards a progressive paraplegia, and death within ten to fifteen years. The lack of an effective remedy further adds to the sinister reputation which this disease has gained. With regard to prognosis, this is more favourable, both for life and disability, than was formerly supposed (Muller, 1949; Allison, 1950; McAlpine and Compston, unpublished). A better understanding of the basic nature of the disease may come, partly from experimental work on encephalomyelitis (Lumsden, 1951), and partly from recent clinical studies. The latter support the view put forward by Ferraro (1944) and others, that a hypersensitivity reaction is responsible for the initial lesion in the central nervous system. This hypothesis suggests that attention to the general health of the patient is of the utmost importance.

History-taking.—In a suspected case of disseminated sclerosis this should have two objects: first to obtain facts about the nature of the patient's symptoms and the course of the illness, and secondly, to inquire into the general health, particular attention being paid to a history of allergy, infection, trauma and emotional upsets, since one or other of these may be associated with the onset of the disease or a relapse.

Correction of physical and psychological abnormalities.—In the early stage of the disease the patient should be admitted to hospital for full investigation, treatment and rest. When the diagnosis is in doubt, the cerebrospinal fluid should be examined, particularly when signs are confined to the spinal cord; in this way cord compression will not be overlooked. The history must be used as a guide in investigating and treating any abnormality in the

general health. If there is a history of allergy, the cause or causes should, so far as possible, be corrected. A high calorie diet should be given if the patient has recently lost weight.

An opportunity should be taken of inquiring into and frankly discussing any cause of emotional tension, since this factor may aggravate symptoms. The necessity for prolonged treatment, attention to general health and avoidance of certain factors tending to lower resistance, such as over-fatigue, infections, loss of weight, and states of nervous tension, should be stressed. Pregnancy has for long been regarded as an important factor in aggravating the disease. Recent studies by Muller (1949), Tillman (1950), and McAlpine and Compston, however, have shown that it does not precipitate the disease and that its effect on the relapse rate is slight. In the case of a young married woman in the early stages of the disease who has not had a child, if the disease settles down under treatment and no major incidences occur for two years, then pregnancy should be allowed; but in a patient with established paraplegia which seriously limits her activities, pregnancy should be discouraged because of the extra strain and fatigue which would result from the care of a young infant. Termination of pregnancy, with or without sterilization, is not, as a general rule, justified unless the disease has reached an advanced stage.

Medicinal treatment.—Until a rational form of treatment becomes available, reliance must be placed on those measures which offer some hope of modifying the course of the disease; among these must be placed the use of arsenic. The following regime has been recommended by Cloake (1947):—

Artificial pyrexia is first induced by four intravenous injections of T.A.B., at intervals of three days. In between injections a course of N.A.B., is given and is repeated annually as follows:—

Intravenous N.A.B.	Number of courses per annum	Details of course
For first 3 years	4	Each course consists of 4 weekly injections: 0.3 g., 0.45 g., 0.45 g., and 0.45 g.
4 to 5 years	3	
6 to 10 years	2	

If the intravenous route is impossible, then six intramuscular injections of sulpharsphenamine should be given in one course.

In between courses of N.A.B., arsenic should be continued in the form of Fowler's solution, 4 minims (0.25 ml.) thrice daily for three weeks in every four. This preparation of arsenic may be used in cases unsuitable for injections of N.A.B.

The assessment of the effects of the above treatment on the course of the disease is difficult, and for this reason no published figures are available. Relapses are not prevented by the use of N.A.B., but it is likely that these may not be so severe or so frequent as in untreated cases. In the established

stage of the disease the value of this form of treatment is more doubtful.

During the past two years *antihistamine drugs* have been on trial at the Middlesex Hospital in the treatment of disseminated sclerosis. Large doses are well tolerated over long periods. It is hoped shortly to publish preliminary results.

Physiotherapy.—This plays an important part in treatment at all stages of the disease. During the patient's stay in hospital graduated exercises for limbs and trunk should be given. On leaving hospital the patient should be provided with an exercise chart, and should be told that daily exercises will contribute towards the maintenance of general health and will diminish the tendency to fatigue. In the stage of established paraplegia much can be done by skilled physiotherapy; re-educative exercises will lessen ataxia. Not uncommonly a patient's range of activity is restricted to a greater degree than is warranted, either through fear of falling or because the patient assumes he can do no better; reassurance and persuasion may result in a marked improvement.

Finally, the maintenance of morale in a paraplegic patient can be greatly helped by means of occupational therapy and social contacts.

PARALYSIS AGITANS

The new antispasmodic drugs which have recently been introduced for the treatment of paralysis agitans have scarcely come up to first expectations, nor is this surprising since medicinal treatment can only diminish muscle tone, speed up movement and, to a slight extent, lessen tremor. In the past the first of these objects has been partially attained by the appropriate use of the atropine group of drugs at a cost of mildly toxic symptoms, such as paresis of accommodation and dryness of the mouth. The action of the newer drugs is similar, although usually these particular toxic effects are slight. At the present time their cost is high and therefore it is questionable whether their routine use is justified, except possibly in combination with the older preparations.

General management.—Whether the Parkinsonian patient be elderly or young, the problem of adjustment confronts him. Unless the degree of disability is considerable, work, except of a heavy manual nature, should be continued for as long as possible. The social life of patients with tremor may become more and more restricted. Here the general practitioner can help to restore confidence. Exercises, graded according to age and degree of disability, are of real value in maintaining activity and morale and preventing stiff joints.

Medicinal treatment.—The following treatment applies both to the post-encephalitic and the idiopathic forms of Parkinsonism. Initially, tincture of stramonium should be given in doses of 15 to 20 minims (0.9 to 1.2 ml.) thrice daily. During the next two months the daily dose is gradually increased, up to 150 minims (9 ml.) if necessary, until mild toxic symptoms appear. Stramonium may also be given in the form of a pill, extract of

stramonium, 1 grain (65 mg.), five to eight times daily. In postencephalitic Parkinsonism, the following mixture may be tried as an alternative: hyoscine hydrobromide, 1/150 grain (0.43 mg.), tincture of stramonium, 25 minims (1.5 ml.), pilocarpine nitrate, 1/32 grain (2 mg.). The last tends to counteract the toxic effects of the atropine group. The dose of hyoscine may be increased to 1/75 grain (0.9 mg.). No drug is available which will control the tremor of paralysis agitans; in some patients stramonium has a beneficial effect, in others phenobarbitone, ½ grain (32 mg.) thrice daily. The mental inertia which often accompanies postencephalitic Parkinsonism may be lessened by amphetamine sulphate or an equivalent drug, in doses of 5 to 10 mg. in the morning and at midday.

The new antispasmodic compounds with an atropine-like action include 'parpanit,' 'diparcol', 'artane' and 'lysivane'.

Trihexyphenidyl (or 'artane') is given in 1 mg. doses four times daily; the dose is gradually increased to 6 to 10 mg. a day, although in some patients as much as 15 to 20 mg. may be necessary.

'Lysivane' (ethopropazine hydrochloride) is a British preparation in the form of 50 mg. tablets. The initial daily dose is 50 to 200 mg.; one or two tablets should be added, at intervals of three or four days, until by the end of four to six weeks a dose of between 200 to 400 mg. (4 to 8 tablets) is reached.

The toxic effects of these new preparations include nausea, drowsiness, lassitude, muscular cramps, and, rarely, a mild degree of mental confusion. These side-effects may be avoided if sufficient care is taken in building up the dosage and maintaining a level short of toxicity. In practice, a combination of tincture of stramonium with one of the above drugs may produce more benefit than when either is used alone.

Surgery has lately come into prominence in the treatment of cases of Parkinsonism with tremor. An incision of the spinal cord (lateral cordotomy) invariably produces some degree of paralysis, which, however, tends to recede. This operation should only be considered in young patients in whom gross tremor is strictly unilateral.

TUBERCULOUS MENINGITIS

So rapid has been the advance of chemotherapy in the past decade that we have come to accept, almost too readily, the remarkable fact that recovery from tuberculous meningitis is now possible. Although the treatment of this condition does not come within the scope of the general practitioner, a short account will be given of the methods used in hospital in order that he may appreciate the important part which he plays in diagnosis.

The Medical Research Council report of 1948 concludes that the recovery rate is highest in cases treated early in the disease. If a young child or adult has had for a week, or even less, fever, headache and vomiting and has appeared irritable, restless and at times drowsy, urgent admission to hospital is desirable, irrespective of whether or not meningeal signs are found.

A history of tuberculosis in the patient or family, or of active tuberculosis in a contact, would strengthen the provisional diagnosis. In hospital the cerebrospinal fluid is examined; in addition to an increase in cells and protein, in an early case of tuberculous meningitis a fall in the sugar content of the fluid is more likely than in the chlorides. The specimen is examined for tubercle bacilli. An X-ray of the chest is taken to exclude miliary tuberculosis.

Assuming that the diagnosis is confirmed, the relatives are informed of the nature of the illness. They are told that treatment with *streptomycin* is intended, that it will last for at least six months, and that the outcome may not be certain even then. Treatment is then begun by the intramuscular and intrathecal routes; for adults the intramuscular dose of streptomycin is 2 g. daily; for a child it is calculated on the basis of 20 mg. per pound (44 mg. per kg.) body weight per day. The intrathecal daily dose by the lumbar route is 100 mg. daily and 50 mg. for children. It will be continued for the first six weeks and thereafter at intervals of two or more days, depending upon the clinical and cerebrospinal fluid findings. Streptomycin by the intramuscular route will be necessary for six months. The majority of patients stand up well to this strenuous treatment. Giddiness and, less commonly, deafness are common sequelæ of prolonged treatment with this drug.

Various additional preparations have been recommended, either to enhance the action of streptomycin, or to prevent the formation of exudate; the most promising of these is a tuberculin preparation 'PPD'; the results of its intrathecal use have been described by Smith and Vollum (1950). There is every likelihood that its use in conjunction with streptomycin will further reduce the mortality rate.

Survival may be expected in 1 in every 4 cases of tuberculous meningitis treated with streptomycin; early treatment will give a higher recovery rate. In the Ministry of Health series (1950), 88 out of 104 survivors were well after 22 to 33 months' observation. Residual symptoms may occasionally persist, but seldom have serious consequences.

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ADVANCES IN ALLERGY

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THE present discussion concerns primarily the more recent advances in therapy in the field of allergy. It may, however, be misleading if one fails to call attention to the fact that knowledge concerning allergic manifestations and their management is by no means of recent origin. The understanding and treatment of allergic disease may be divided into three periods.

The first period comprises chiefly the nineteenth century, but dates back as long as two thousand years.

In his treatise 'On Asthma', published around the middle of the nineteenth century, Henry Hyde Salter (1859) describes a number of remedies for asthma, some of which are still in use today. Among these are ipecacuanha, tobacco, iodides, stramonium, coffee, alcohol, chloroform and nitre. Salter (1859) and Bree (1811) call attention to a number of specific causes of asthma, which include foods, ipecacuanha powder, animal emanations, hair powder (orris?), musty odours (molds?), and wood smoke. In the same century Charles Harrison Blackley (1873) established pollen as a cause of hay fever and attempted immunizing treatment. During the nineteenth century John Bostock (1819) described hay fever as a clinical entity; John Elliotston (1831) claimed that it was due to pollen; Blackley made extensive researches proving that pollen is the cause of hay fever; and Morrill Wyman (1872) showed that ragweed pollen is the major cause of hay fever in America. As early as the seventeenth century such gifted clinicians as Joannes Baptista van Helmont (1707), Thomas Willis (1681), and Sir John Floyer (1698) expressed a clear understanding of the nature of asthma. As a matter of fact, as early as in the second century A.D., Aretaeus gave a graphic description of asthma. And in the Ebers Papyrus (Sobhy, 1934) there is found a series of prescriptions, which include the inhalation of the smoke of burning drugs for the relief of what was probably asthma.

The second period comprises the time from the turn of the twentieth century until recently. During this phase of progress our most important anti-allergic and anti-asthmatic drugs, such as epinephrine, aminophylline and ephedrine were introduced.

The demonstration of the principles of anaphylaxis led Noon (1911), and Freeman (1911), to the application of desensitization procedures in hay fever. A few years later desensitization to unavoidable inhalant substances became a routine procedure in the treatment of allergic disease. Schloss, in 1912, established skin tests as a diagnostic procedure in allergy. The sensitizing antibody, the reagin, was demonstrated by Prausnitz and Küstner in 1921. Later, it was shown (Cooke *et al.*, 1935) that a blocking or neutralizing antibody is produced by desensitizing injections. During this period also there were discovered new specific causes of allergy, and old ones were re-studied and the knowledge concerning them extended. Among these may be mentioned fungi (Feinberg, 1935), house dust (Cooke, 1922), pollen and contact substances. This period was notable for the gradual recognition, acceptance, and extension of the practical applications of allergy. There was also the beginning of application of newer concepts of allergy, resulting in extension of the field to such conditions as drug hypersensitivity, infectious disease, and collagen syndromes. At the close of this period allergy had become an established mode of successfully managing many human ailments.

The third and last period embraces the last five or six years. This period has seen advances in somewhat different directions.

SYMPATHOMIMETIC AND OTHER DRUGS

Isopropyl epinephrine (Gay and Long, 1949), known in Great Britain as isoprenaline sulphate, and in the United States as 'isuprel' and 'norisodrine,' has become one of the most important drugs for the relief of the asthmatic attack. Its most common mode of use is the nebulization of a 1:200 or 1:100 solution with the hand nebulizer. At times the insufflation of a diluted micronized powder from a special small gadget may be more effective. The bronchodilatory effect of this drug is about equivalent to that of epinephrine, with each being more effective than the other in individual cases. The chief advantage of isopropyl epinephrine is due to the fact that it does not possess the vasoconstrictor or pressor effect of epinephrine. It should be emphasized that one major toxic action is common to both drugs—the ability to produce cardiac stimulation. Caution in the use of the drug is necessary, and its administration other than topically, such as by linguettes, is not advised.

Orthoxine, or orthomethoxy-beta-phenyl-isopropyl methylamine hydrochloride (Curry *et al.*, 1949) is another bronchodilator which has recently become quite popular. Its action is much like that of ephedrine but it possesses less of the pressor and cerebral excitatory effect than the latter. It is, however, also less potent, and a dose of 100 mg. is the one most commonly employed. Even with that amount it is not as effective as 25 mg. of ephedrine, but has its greatest usefulness as a prophylactic in persistent asthma.

Clopane, or 1-cyclopentyl-2-methylamino-propane hydrochloride (Gouze, 1951), is a drug possessing some of the vasoconstrictor action of ephedrine with less of the cerebral excitatory effect. It is useful particularly in the obstructive stages of hay fever and in perennial vasomotor rhinitis. A common preparation on the market consists of a capsule containing 50 mg. of clopane in combination with 25 mg. of an antihistamine.

The possible usefulness of several other drugs deserves mention. Khellin (Derbes *et al.*, 1951) has been advocated as a bronchodilator, but still needs more extensive investigation. 'Demerol' is useful at times in asthma, but has some of the objections of other hypnotics—suppression of cough reflex and danger of addiction. Procaine intravenously in urticaria and asthma holds some possibilities, but the hazard of allergy to this drug must be considered. Various vasoconstricting solutions for nasal use have been marketed, but the general objection to the use of such nose drops still prevails.

HISTAMINE

The establishment of the rôle of histamine in the mechanism of the allergic reaction has led to a widespread attempt to employ histamine injections in the treatment of allergy, with the notion that desensitization to histamine

would be accomplished thereby. However, both in animals and man it has been shown that the tolerance to histamine in the individual remains unaffected even by prolonged treatment (Dannenberg and Feinberg, 1951). If histamine injections do produce therapeutic results they probably do so by virtue of other mechanisms, such as periodic exercise (dilatation and constriction) of the blood vessels. The conjugation of histamine to a protein has been no more effective in producing a tolerance to histamine (Hebald *et al.*, 1947). If such a compound does on occasion produce a therapeutic effect it is most likely due to the non-specific action of the protein or to psychic suggestion. Although histaminase is able to destroy histamine *in vitro* it was not found effective in the living animal or man (Rostofer and Laskowski, 1945).

THE ANTIHISTAMINES

As a means of combating histamine the antihistaminic drugs have constituted an important advance in the last few years. The precursors of the drugs in present use date back many years, particularly to the researches at the Pasteur Institute. As a result of these investigations 'antergan' was the first antihistamine deemed to have a therapeutic/toxicity ratio sufficiently favourable for human use. 'Antergan' was soon replaced by a number of other drugs. As is now pretty generally known the antihistamines as a whole possess certain properties (Feinberg *et al.*, 1950), among which are the prevention of histamine and anaphylactic shock in animals, the prevention of the histamine wheal and flare in man, diminution of most of the histamine-induced symptoms in man, inhibition of some of the phenomena of allergy, a local anæsthetic effect, the production of excitatory phenomena in animals, and the initiation of sedative or excitatory symptoms in man (depending on the dose, individual subject, and specific antihistamine).

The antihistamines have found their greatest sphere of usefulness in the nasal allergies (Feinberg *et al.*, 1950). In seasonal hay fever and in non-seasonal vasomotor rhinitis most of these drugs are at least partially effective in more than half of the cases. In allergic cough they may be helpful, whereas in asthma their action is usually far inferior to that of the other accepted remedies. In urticaria, angioneurotic œdema and drug reactions they usually give considerable relief from the itching, even though the swellings may often be undiminished. In atopic dermatitis (neurodermatitis), contact dermatitis and dermographism the antihistamines are often useful. In a number of other pruritic conditions these drugs may be helpful. In some cases of gastro-intestinal allergy or allergic headache the antihistaminic drugs may exert a desirable effect. However, in a number of conditions for which benefit had been claimed earlier, subsequent developments have indicated that these drugs are not effective. Both in the experimental animal and in man the therapeutic effect in tuberculosis has been disproved (Millner and Hurst, 1949). There has been no significant benefit in any of the other bacterial allergies, nor in the collagen diseases. The earlier claims for the prevention or cure of infectious colds by antihistamines have been

refuted by well-controlled experiments conducted in England and in the United States (Paton *et al.*, 1949; Hoagland *et al.*, 1950).

The antihistamines are generally administered orally, either as needed or at regular intervals several times daily. With the majority of the drugs a 50 mg. dose is the average for adults, whilst children's doses are reduced usually not as much proportionately as in the case of most other drugs. The less potent antihistamines such as 'neohetramine' and 'antistine,' require doses of 100 mg. or more for appreciable effect. The usual dose of 'phenergan' is 12.5 mg., whilst that of 'chlortrimeton' is 4 mg. The duration of effect of the average dose for most antihistamines is four to six hours. Chlorcyclizine ('di-paralene' or 'perazil') may give an effect for about twelve hours. 'Phenergan' may produce relief for as long as twenty-four hours. At times the antihistamines are combined with aminophylline, ephedrine or amphetamine for synergistic effect or to combat the sedative action of the former. Enteric-coated tablets may be used to advantage at bedtime. Hypodermic or intravenous medication is indicated as a rule only when more rapid results are required, in emergency measures, or when gastric tolerance is poor. The most common drug used hypodermically is 'benadryl', in a dose of 10 to 50 mg.

Topical treatment with antihistamines may also be used in certain manifestations. In allergic conjunctivitis drops of a mild antihistamine (usually 0.5 per cent. of 'antistine') may give relief. For the nose, drops of 0.5 per cent., or preferably a spray of 0.5 to 1.0 per cent., of 'pyribenzamine', may be effective in the resistant stages of vasomotor rhinitis (Zeller, 1949). Not infrequently, however, the local use of these solutions will cause irritation. A nebulized solution of 2 per cent. 'pyribenzamine' may be effective in some cases of allergic cough or asthma (Feinberg and Bernstein, 1949). For itching dermatoses, such as atopic dermatitis, contact dermatitis, pruritus ani or insect bites, ointments or creams of antihistaminic drugs may be desirable (Feinberg and Bernstein, 1947). However, in acute and in many of the chronic dermatoses local use of antihistamines may increase the irritation and even produce specific contact allergies.

From what has already been said it will be apparent that the usefulness of the antihistaminic drugs is hampered by a number of limitations. At best a single dose is effective for only a few hours at a time. They are not greatly effective in some allergies, such as asthma or the bacterial allergies. They are virtually without value in the common cold. In those manifestations, such as hay fever, in which they display their greatest effectiveness, many persons with mild symptoms, and most with severe symptoms, fail to obtain satisfactory relief. They do not replace allergic management or desensitization therapy, but are useful as an adjunct. As shown by our objective studies (Dannenberg and Feinberg, 1951) the development of tolerance to antihistamines after their regular use is common. One of the most important limitations to the use of antihistamines is their toxicity; the incidence of such toxic reactions from therapeutic doses varies from about 10 to 50

per cent. among the different drugs. The most common side-action of the vast majority is some form of sedation, varying from a slight calming of nerves to severe hypnotic effect. This may manifest itself as sleepiness, diminished alertness or inability to concentrate. It may constitute a safety hazard in some instances. Excitation is manifested in some persons with moderate doses, in all with excessive doses, and in the case of one of the drugs ('thephorin') it is the characteristic toxic effect. Excitation may take the form of nervousness, insomnia, nausea, palpitation, irritability, muscular tremor and, in extreme cases, usually with large doses, convulsions and hyperpyrexia. Fatalities at this stage have been recorded. Other toxic effects are gastro-intestinal disturbances, occasional skin rashes, and rarely an instance of blood dyscrasia.

The multiplicity of individual antihistamines and the claims and counter-claims of their promoters have created some confusion in the mind of the practitioner. If the physician will acquaint himself with one drug from each of three classes he will find that one or the other of such three antihistamines will be suitable for the majority of patients who respond to antihistaminic drugs. For this purpose the drugs may be divided into three groups:—

Group 1 comprises the less sedative drugs: 'antistine', 'neohetramine', 'thephorin' and chlorcyclizine ['di-paralene', 'perazil']. Group 2 is composed of the moderately sedative members and includes 'chlorothen' ['tagathen'], 'chlortrimeton', 'diatrin', 'histadyl' ['thenylene'], 'neoantergan' ['anthisan'], 'pyribenzamine', 'pyrrolazote', and 'trimeton'. Group 3 includes the highly sedative 'benadryl', 'decapryn', and 'phenergan'.

ADRENOCORTICOTROPHIC HORMONE (ACTH) AND CORTISONE

A number of observations has constituted the background for expecting therapeutic benefit from ACTH and cortisone in allergic disease. The use of these hormones in asthma and other allergic manifestations has become so widespread and abused in the United States that our British colleagues may well profit by a clear statement of our errors and misdirections.

The greatest usefulness of these hormones in allergic disease is in the treatment of acute status asthmaticus (Cooke *et al.*, 1951; Feinberg *et al.*, 1951; Randolph and Rollins, 1950; Rose *et al.*, 1950). In such situations the hormone will usually effect a dramatic improvement within twenty-four to forty-eight hours. In acute, severe, but self-limited allergic conditions, such as severe penicillin and other drug reactions, these agents are helpful and may be indicated (Carey *et al.*, 1950). They may possibly be justified in some short-term allergies such as ragweed hay fever (Carryer *et al.*, 1950). However, the prevailing experience indicates that the effect of such hormones is temporary and that prolonged use is not only prohibitive in cost but may be hazardous. Therefore these drugs are rarely indicated in chronic asthma or in most of the other allergic conditions.

Since there are some contraindications to the use of these hormones, precautionary measures are observed to exclude such conditions as diabetes, cardiac failure, psychoses, acne, and febrile and infectious states.

The patient is placed on a low-salt diet and his weight observed daily, if possible. In acute asthma, the initial dose of ACTH is usually 20 mg. every six hours. In some instances we have had to increase the dose to as high as 320 mg. daily before results were obtained. In most cases a daily dose of 80 to 120 mg. was sufficient. After about forty-eight to seventy-two hours the subjective relief and objective respiratory findings will usually show such marked changes that the dose may be reduced. This is done gradually, first reducing the doses, then increasing the intervals so that the total course of therapy lasts for about six to ten days. This scheme will carry most patients through the acute status asthmaticus. Of course, there is the tendency for the asthma to recur within a day to several weeks after discontinuance of the therapy. In selected cases it has been found expedient to carry the patient along on hormone therapy if small maintenance doses will suffice. Cortisone has also been used, and although in occasional instances this drug has been effective when ACTH has failed, the latter has usually been more reliable. The initial doses of cortisone are usually a total daily dose of 200 to 300 mg. given in two to four intramuscular injections or four oral administrations. The normal maintenance dose is 100 mg.

It is obvious that these hormones have limitations in their use in allergic disease. To their usual hazards may be added that of possibility of severe allergic reactions which have been noted in the case of ACTH (Feinberg *et al.*, 1951). Because of their tendency to diminish pain, abolish fever and elevate the leucocyte count, infectious disease may be masked. Since these hormones reduce local tissue response they may prevent wound healing and promote the dissemination of infectious agents. In questionable situations it may be advisable to employ antibiotic therapy along with the hormone administration. These drugs are not curative, nor do they need to be used in the vast majority of instances of allergy. In most allergic patients simple palliative treatment or elimination of the allergen or desensitization is the more effective and more rational approach.

In an attempt to show objectively the effect of these hormones in allergic disease we have made a number of studies (Feinberg *et al.*, 1951). The sensitizing antibodies have remained unchanged as a result of ACTH or cortisone therapy. Quantitative studies of the skin reaction to histamine and antigen also failed to show any effect. It is possible that the shock organ, for example the bronchi in asthma, may be affected by these hormones, whereas the skin or any other tissue exclusive of the shock organ remains unaffected.

PSYCHOTHERAPY

The last few years have witnessed a rapidly growing application of the concept that much of somatic derangement springs from psychogenic disturbances. Asthma, urticaria, vasomotor rhinitis and similar conditions have been included in the catalogue of manifestations dependent upon psychic stimuli (Abramson, 1951). There are three major attitudes to this question. One is the view held by a group of extremists who believe that every so-called allergic manifestation is directly traceable to such situations as maternal rejection, self-absorption, fear of suffering, inferiority complexes, family conflicts, desire for attention and other emotional abnormalities. This school will go so far as to deny the existence of allergy or the influence

of the allergic reaction in the production of asthma and similar phenomena. A second attitude, assumed particularly by some allergists, is that the allergic reaction is the only stimulus responsible for asthma, vasomotor rhinitis or urticaria, and that such factors as infection, physical, chemical or emotional stimuli play little if any part in the production or aggravation of these diseases.

There is also a third attitude, which is held by an increasing number and is in conformity with long and large experience in observing allergic persons by myself and others. This concept regards the rôle of psychogenic stimuli, as well as thermal, physical and chemical stimuli, to be usually secondary in nature, that is, they activate an already existing allergy, thus initiating an attack or making the manifestation worse. It is further apparent that the association of emotional and personality conditions with allergy is more often the result of the latter than the cause. It is not denied that it may be possible for autonomic stimuli initiated by higher centres to release histamine or other mediators to produce urticarial wheals or similar reactions ordinarily regarded as allergic. However, for proof of such a mechanism close cooperative research will need to be done. The work of Graham and his associates (Graham, 1951) is a good beginning in this direction.

THERAPY BASED ON IMMUNOLOGICAL PRINCIPLES

The third period has also seen a reawakening of interest in the pursuit of investigation of basic immunology, some of which may ultimately have practical application to therapy. Studies of the nature of antigens, their origin, and their mechanism of action are among such researches. Attempts at purification of antigens and modifying them with the viewpoint of enhancing and perfecting the immunity response, are among the investigations which may lead to improvement and simplification of therapy. The question of food allergy has undergone a Jekyll and Hyde existence in the last few years. A small group of advocates see in food allergy the explanation, not only of most allergic manifestations, but also of many syndromes ordinarily not identified etiologically (nervousness, fatigue, weakness, muscle pains, psychoses). This school claims that the most refined food products, such as corn dextrose, cane sugar, beet sugar, and vegetable oils, carry the antigenicity of the original food source and are responsible for much of allergy. The majority opinion, however, based on large experience, controlled tests and animal experiments, does not agree with the above. Furthermore, in the last few years most specialists have come to regard foods of less importance than considered previously. Bacterial allergy is a field which is having a revived attention from investigators. Whilst developments thus far have produced no radical therapeutic changes, the potentialities are intriguing.

SUMMARY

Advances in the therapy of allergic diseases in the last few years have been mainly along the lines of new sympathomimetic drugs, the antihistamines,

ACTH and cortisone, and more rational approaches to psychotherapy. There is a tendency to over-emphasize the new and to disregard the old and more established therapeutic methods. The recent developments have not served to change radically the problem of the management of allergic disease. Specific allergic management along the lines of recognition of specific causes, their elimination or desensitization to them, still remains the mainstay in the handling of the allergic patient. Recently there is increasing impetus in the study of basic principles in immunology with the hopes of applying newly gained knowledge to the improvement of therapy of allergic disease.

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ADVANCES IN THE TREATMENT OF VIRUS DISEASES

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TEN years ago the specific treatment of virus diseases was limited to the use of various drugs, including the sulphonamides, in patients with lymphogranuloma venereum. The recent advances in the production of antibiotics, however, has resulted in the satisfactory specific treatment of infection with the rickettsiæ and some of the larger viruses. Newer knowledge of the mechanism of growth of certain other viruses has cast a ray of hope on the successful treatment of the virus diseases in general in the not too distant future.

The inherent difficulty of attacking viruses with drugs, chemicals or antibiotics, lies in the fact that the life of the virus is integrally bound to the internal structure and life of certain tissue cells of the host, on which it draws for the synthesis of its protoplasm. Thus, broadly speaking, interference with the growth of the virus may of necessity interfere with the life of the cell, and there is obviously a limit to the degree of damage which individual cells can suffer and yet survive and the number of cells which can be safely destroyed in the attempt to kill the virus. It is probable that each virus or group of viruses undergoes a different life-cycle or process of multiplication, with the result that different interfering substances may be necessary for the different viruses. The smaller viruses, like poliomyelitis, which may be most dependent upon pre-formed substances in the cell for their development, may be less exposed to attack. Efforts along these lines of interference in the life-cycle are still in the experimental stage in the laboratory, but the possibilities of this method of attack have been exemplified by (1) the reduced susceptibility of mice on a thiamine-deficient diet to the Lansing strain of poliomyelitis virus; (2) the inhibition of growth of a pneumonia virus of mice by certain bacterial polysaccharides; and (3) the inhibition of growth of the mumps virus in chick embryos by the addition of a particular bacterial polysaccharide. The antibiotics which have already been found to be effective in the treatment of the rickettsial and certain virus diseases have, in fact, not killed the organisms but only suppressed their growth sufficiently for the body to survive while immunity is developing to a degree when the infection is curtailed.

Before dealing with the treatment of specific virus diseases I should remind practitioners that vaccines and antisera are available, or are being developed, for prophylaxis in a number of rickettsial and virus diseases

affecting man. Apart from the well-known vaccines which have been used successfully against influenza, rabies, smallpox and yellow fever, vaccines against equine encephalomyelitis, Japanese B encephalitis and mumps are being investigated and, of course, some kind of vaccine for poliomyelitis is a hope for the future.

Specific antisera have not been found effective in the treatment of human virus diseases, but the effect of early administration of hyper-immune serum in rabies is being re-examined. Convalescent serum or the gamma globulin fraction of adult serum may, however, be used in the prophylaxis of measles or rubella, and gamma globulin in infective hepatitis. The use of such sera is usually indicated only for attenuation or prevention in sickly children or for special administrative reasons. Because of the susceptibility of the young fœtus to the virus of rubella, pregnant women exposed for the first time to rubella during the first four months of pregnancy should receive prophylactic treatment; for this purpose gamma globulin from the plasma of recent rubella convalescents is obviously desirable but is, unfortunately, in very short supply. Doctors who can persuade adult patients with rubella to donate a pint of plasma in the fourth to sixth week of convalescence should do so.

The use of immune serum is unwarranted in the treatment of post-vaccinal and post-infectious encephalitis; these conditions are most probably due to allergy and treatment with the antihistamine preparations has been advocated.

RICKETTSIAL DISEASES

All types of typhus can now be controlled by the administration of aureomycin or chloramphenicol, but relapses may occur when treatment is begun very early in the illness (Smadel, 1950). The dosage suggested for Q fever is applicable to all members of the typhus group.

The rickettsial diseases in general are of little importance in Great Britain, but *Q fever* may be encountered in England and Wales. The causative organism, *Rickettsia burneti* (sometimes known as *Coxiella burneti* because of certain differences it possesses from other rickettsiæ), is fortunately held in check, but not killed, by the new antibiotics, chloramphenicol, aureomycin and terramycin. Although the disease carries a very low mortality rate, it may cause a debilitating illness. A recent paper by Clark *et al.* (1951), based on the treatment of 45 patients with aureomycin, suggests that 4 g. orally per day for five days, together with intravenous doses of 100 mg. two or three times daily for four or five days, will result in defervescence on the sixth day and clinical recovery, but occasionally patients may not respond rapidly even with this dosage. However, for general use the oral dosage will probably be satisfactory. Laboratory workers likely to come in contact with this highly infectious agent can be immunized effectively by three injections at seven-day intervals with a formalinized suspension of *R. burneti* in infected yolk sacs of chick embryos.

VIRUS DISEASES

Psittacosis-lymphogranuloma venereum group.—The only members of the virus family which have been proved conclusively to be affected by chemotherapy or antibiotics are those of the psittacosis-lymphogranuloma venereum group. This characteristic is one of several which has tended to set this group slightly apart from other viruses. The growth of certain members of this group in mice and eggs may be checked, even if the organisms are not killed, by sulphonamides, penicillin and the newer antibiotics. Cases of lymphogranuloma venereum have improved by treatment with pentavalent antimony and sulphonamides, but chloramphenicol and aureomycin are more effective. The latter has been reported to cure both the primary lesion and proctitis (Wright *et al.*, 1948; Wammock *et al.*, 1950), but Robinson *et al.* (1950) recorded disappointing results. The treatment suggested by Nicol (1951) is aureomycin or chloramphenicol, 2 g. daily for ten days, in patients with the inguinal syndrome, and the same dosage for twenty days in patients with proctitis. Human infection with psittacosis virus is very rare in Great Britain, but when it occurs it may be severe. Treatment with large doses of up to 2 million units of penicillin in twenty-four hours may be of value, but aureomycin is preferable. Fortunately, ornithosis virus infection, which probably comes from pigeons or domestic fowls and is much more common than psittacosis, appears to produce a less severe illness in man but may occur as primary atypical pneumonia, when patients will probably benefit by treatment with aureomycin, 1 to 4 g. a day. This substance has also given promising results in trachoma (Freyche, 1950), which is caused by a virus of the same group; but whether its action here is on the virus or on secondary bacterial infection remains to be determined (Shah, 1951).

In none of the other virus diseases has chloramphenicol, aureomycin or terramycin been proven to be specific, although it is undoubtedly true that they may be of considerable value in checking the bacterial infection which often accompanies and complicates certain skin conditions of viral etiology, influenzal pneumonia, and primary atypical pneumonia.

VARICELLA ZOSTER

Finland and his colleagues (1949) in the U.S.A. were optimistic about the value of these antibiotics in the relief of pain and the abortion of lesions in zoster, but a number of cases of varicella or zoster have occurred in patients under treatment with these antibiotics for some other condition. Recently, Carter (1951), in Great Britain, in an investigation of 44 consecutive patients consisting of 4 groups of 11, including one treated with glucose capsules as controls, found that aureomycin in a dosage of 2 g. daily for six days, or 4 g. daily for four days, or chloramphenicol, 2 g. daily for six days, showed no superiority over the control treatment as regards relief of pain, paræsthesia, or appearance of fresh lesions. The treated groups were, of course, free from secondary infections, and this probably helped in the more rapid drying up

of the lesions. In recent correspondence on this controversial subject, in which they describe a case of ophthalmic zoster which appeared to benefit from treatment with chloramphenicol and atropine drops, Hodgson *et al.* (1951) suggested that zoster may be caused by one of two viruses, one being susceptible to chloramphenicol and the other not. There is, of course, no susceptible experimental host for varicella or zoster viruses, so the final assessment must be made on results in man.

VARIOLA VACCINIA

The antibiotics are highly effective in keeping the skin lesions bacteriologically sterile, but Anderson *et al.* (1951) found that penicillin (3 cases), aureomycin (3 cases), and chloramphenicol (1 case) had no effect on the specific illness in smallpox.

HERPES SIMPLEX

Infection with herpes simplex virus in chick embryos and experimental animals has been unaffected by aureomycin and chloramphenicol, and claims of successful treatment in man have not been convincing. The course of the disease is of such a nature as to make evaluation of therapy difficult, but Buerk and Blank (1951) have recently given a very clear description, with the results of virus studies, of acute *disseminated herpes simplex* in an adult, which was unaffected by 250 mg. of aureomycin four times a day for ten days, beginning on the second day of the disease, plus 300,000 units of penicillin twice daily.

INFLUENZA AND INFLUENZAL PNEUMONIA

There has been no satisfactory inhibition of the growth of influenza viruses A or B in chick embryos or experimental animals with substances which can be used for the treatment of human infections. A controlled study by Thalmann *et al.* (1950) on the use of aureomycin in 69 patients and penicillin in 43 patients compared with 38 untreated patients, all occurring in a localized outbreak of influenza A in an army camp during the winter of 1949-50, revealed no advantages from the use of antibiotics. On the other hand, Finland and his colleagues (1949) reported that the use of aureomycin in 18 cases of influenza was followed by rapid improvement and relief of symptoms. These cases differed from Thalmann's in that they were selected for aureomycin treatment because of their severity, usually as the result of pulmonary complications. Exactly on what the aureomycin is acting is still in doubt, but it may well be on penicillin-resistant strains of bacteria which are secondary invaders. Certainly penicillin-resistant staphylococci have been identified in, and suspected as the cause of death in, a number of rapidly fatal cases of virus influenza with pneumonia in recent epidemics. The dosage will be the same as in Q fever, or the drug may be given orally in doses of 0.25 g. every six hours, accompanied by a daily dose of 600,000 units of penicillin intramuscularly. Thalmann and his colleagues found that

this dosage was better tolerated than 4 g. a day, and serum levels were found to be not much lower than in those receiving larger doses.

PRIMARY ATYPICAL PNEUMONIA

The situation is somewhat the same here as in influenzal pneumonia. It has been reported by Collins *et al.* (1950), and Meiklejohn and Shragg (1949) that aureomycin and chloromycetin hasten the recovery of patients with this complaint. They suggest that the action is on a specific virus agent, but this remains to be proved. The dosage will be as for influenza, and Thalmann *et al.* (1950) recommend small doses.

POLIOMYELITIS

One of the diseases on which most attention is being focused, but in which the virus may be most difficult to affect, is poliomyelitis. The virus in the form in which we can study it is only 8 to 12 mμ in its smallest diameter, i.e., about 1/25 the size of the members of the psittacosis group. A trial of aureomycin, 2 to 6 g. a day (depending upon age), for five days, by Appelbaum and Saigh (1950) on 38 patients in the preparalytic stage in New York in 1949, showed no benefit as compared with 66 untreated control patients admitted during the same period. However, only two of the treated group and none of the controls developed paralysis, so a larger group of patients would need to be examined to give a conclusive answer on the effect at this stage. The course of the illness was unaffected in 20 paralytic patients.

ACTH was used in a controlled trial in U.S.A. by Coriell *et al.* (1950) with 35 patients treated and 35 controls, including approximately the same number of cases of non-paralytic, spinal paralysis and bulbar paralysis in each group. There was no demonstrable effect as measured by temperature response, paralysis, progression of paralysis or early residual effects. There was also no effect on the degree of spasm, pain and tenderness or the duration of the sensitive stage.

HEPATITIS AND CIRRHOSIS

Apart from its direct action on the etiological agents, aureomycin may also have an indirect effect on disease processes and the nutritional state of animals and man. In acute viral hepatitis treated within seven days of the appearance of jaundice, aureomycin appeared to have little immediate effect, but there was suggestive evidence that the late manifestations of the disease might to some extent be controlled (Shaffer, Farquhar *et al.*, 1950). Use of the antibiotic in rats fed on a hepato-necrogenic diet suggested that aureomycin, by inactivating the intestinal flora, prevented the organisms themselves, their toxins, or the products arising from their action in the intestine, from passing to the liver, which was already damaged by the action of the virus, thus giving the liver cells a better chance to recover. Certain patients with chronic liver disease or in hepatic coma appeared to benefit from

administration of aureomycin, but some others did not respond (Shaffer, Bluemle *et al.*, 1950; Farquhar *et al.*, 1950).

SUMMARY

This short account indicates that rickettsial diseases and diseases caused by viruses of the psittacosis-lymphogranuloma venereum group may be treated successfully with aureomycin or chloramphenicol. The use of these antibiotics may be indicated in other virus diseases to combat an accompanying bacterial infection, but their specific action on the viruses is as yet not proven.

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ADVANCES IN THE TREATMENT OF SKIN DISORDERS

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RECENT advances in the treatment of skin disorders have followed closely behind advances in diagnosis and an ever increasing knowledge of the physiology and pathology of the skin. This progress has been dependent upon the following factors: the use of new antibiotics, the antihistamine drugs, and a wider range of radiation therapy; increasing knowledge of the important part played by the mind and emotions in disorders of the skin, and a more accurate assessment of the influence of disorders of metabolism and hormone production; greater knowledge of the influence of deficiencies of vitamins, and the closer combination of clinical, histopathological, mycological, bacteriological and allergic examination. All this is accompanied by greater attention to overcome the occupational hazards experienced in industry and the home, and to the protection of the skin by the use of barrier creams, against the effects of detergents, paraffin, oils and many chemicals.

SYSTEMIC ANTIBIOTIC TREATMENT AND CHEMOTHERAPY

Penicillin has revolutionized the treatment and prognosis of some disorders of the skin. The time required to effect a cure has been materially shortened by the use of systemic penicillin therapy and local applications of penicillin sprays and lotions. Its potency against a wide range of organisms is well known, and certain clinical pictures, such as impetigo and sycosis barbæ, have as a result become less common and more quickly cured. Its bacteriostatic and bactericidal effect is of great value in such cases as erysipelas, folliculitis, furunculosis, cellulitis and, to a lesser extent, in exogenous dermatitis, traumatic and static ulcers, and (secondarily bacterial) infection of disseminated cutaneous herpes simplex (Kaposi's varicelliform eruption). Whenever possible, the sensitivity of the micro-organisms should be determined before starting treatment. It is well to remember that hypersensitivity reactions to antibiotic therapy are most likely to occur in patients with an hereditary predisposition to allergic disorders in general (atopic subjects). Too small doses of systemic penicillin over too short a period, or prolonged use of ointments or lotions are common errors. The systemic dosage recommended is 600,000 units of procaine penicillin in oil by intramuscular injection once daily for five to seven days (Mitchell-Heggs, 1950).

Aureomycin, given in doses of 500 mg. *statim* and 250 mg. six-hourly, appears to be valuable for the early treatment of herpes zoster, and should be given in all cases with ophthalmic involvement. The incidence of post-herpetic pain is not necessarily reduced. Severe cases of erythema multiforme

with mucosal lesions (the so-called Stevens-Johnson syndrome) are reported to have resolved rapidly. The results in dermatitis herpetiformis have been encouraging, with marked relief of itching and involution of the vesicles within one or two weeks of treatment, but there is a tendency to recurrence of the disease after the treatment has been stopped. All the cases I have seen have recurred.

Chloramphenicol.—This is now available in this country and the toxic effects are minimal. Oral therapy has been found effective against a wide range of bacteria and some of the larger viruses, such as that causing lymphogranuloma venereum. Herpes zoster has been reported to respond when treated early, and some cases of aphthous buccal ulceration do well. There is always the danger of destruction of bacterial flora in the intestines, and the incidence of glossitis, gastritis, pruritus ani and other disorders in this treatment, but these complications can be prevented by giving generous doses of vitamin B complex.

Streptomycin.—The combination of streptomycin and sodium *para*-aminosalicylic acid (PAS) can be used in treating cases of lupus vulgaris which have proved unresponsive to calciferol. It is best to give the first course to the patient while he is in hospital or in bed at home and under a specialist's advice. The side-effects of streptomycin should always be considered, especially the effect on balance, hearing, and also the possibility of the development of a streptomycin-resistant strain if the dosage is inadequate. Some cases of erythema induratum (Bazin's disease) and rosaceous tuberculide respond to a combination of streptomycin, 1 g., and PAS, 15 to 20 g., daily for a first course of ten days.

Sulphonamides.—The use of sulphonamides has now fallen into perspective after an initial surge of enthusiasm, and they have become less popular, but there is no doubt as to their effectiveness in combating coccogenic dermatoses. Erysipelas, pustular folliculitis barbæ with lymphadenitis, certain cases of pustular acne vulgaris, and secondarily infected seborrhœic dermatitis respond to treatment with the new sulphonamides. Sulphapyridine in relatively small doses of 0.5 g. thrice daily has proved effective in controlling dermatitis herpetiformis. The mode of action of the drug in this disorder is not clear as micro-organisms have not been shown as the causative factor. In certain patients this treatment has been more effective when combined with antihistamine drugs, particularly 'pyribenzamine'. Occasionally, the sulphonamides will initiate an eruption like seborrhœic dermatitis and may aggravate a proven case. It must be remembered that sulphonamide therapy, applied locally as an ointment or lotion, may be followed by hypersensitivity to sunlight. Sensitization by topical therapy is rare in children before the age of puberty (Sulzberger and Baer, 1950).

LOCAL ANTIBIOTIC TREATMENT

Topical penicillin therapy has little place in the treatment of skin dis-

orders. Creams and ointments are so often liable to produce local sensitivity reactions in the form of long-lasting skin rashes, which may recur in later years if it becomes necessary to administer penicillin or sulphonamides in a serious illness such as pneumonia. A possible exception is the use of a penicillin lotion in cases of impetigo, 5000 units per ml., as a spray four-hourly for not more than five days. An infected eczema is likely to be aggravated by topical antibiotic therapy. Aureomycin, 3 per cent. in a vanishing cream base, has been found useful in penicillin-resistant cases of folliculitis barbæ and, so far, I have seen no cases of topical sensitivity. This cream is also useful in cases of herpes simplex of the lip. Good results in this condition have been obtained when aureomycin in a water-soluble methyl cellulose base has been painted as a film over the affected area (Kalz, Pritchard and Surkis, 1949). The assessment of the value of treatment in disorders with a known limited duration is, of course, most difficult and inaccurate.

ANTIHISTAMINE DRUGS

Systemic therapy with antihistaminics gives symptomatic relief in most cases of urticaria, certain cases of endogenous and exogenous eczema, and a few cases of erythema multiforme. The sedative effect is often most helpful when irritation is a troublesome symptom in pityriasis rosea, lichen planus, and in occasional cases of senile pruritus. Ano-genital pruritus is a distressing symptom, often without physical cause. In those cases in which psychogenic factors predominate at the outset, structural changes occur in the skin as a result of scratching and perpetuate the symptom. Local antihistamine preparations in the form of an ointment or cream may break the vicious circle. Acute urticarial reactions, such as those following penicillin injections, usually respond well, as does chronic urticaria, but these conditions are not relieved by local antihistamine therapy. A search for the cause and its elimination should be made *pari passu* with this therapy. Generous doses are necessary for the first few days, but a reduction in the dosage is advisable later on when side-effects, such as drowsiness, giddiness, dryness of the mouth and, perhaps, nausea and vomiting, may become apparent. Generalized atopic eczema of the flexural type (disseminated neurodermatitis) and the exudative extensor type respond less readily to antihistamine drugs. I always try these drugs in succession because so often one of them succeeds in a particular case when others have failed. Itching in contact dermatitis is often relieved, but the condition as a whole does not benefit appreciably from these drugs unless removal of the cause is possible.

Dosages of antihistamine drugs depend upon the patient's tolerance to antihistaminics and the relief of their symptoms. It is always advisable to try the generally accepted dose in the first instance and to increase this if necessary. As a rule, the response to the drug is prompt in acute cases, but if this is not noted within three hours, an increase of the dose is indi-

cated. Double the normal amount is sometimes required to produce the desired clinical relief. For 'antistin', 'anthisan', 'histantin', 'phenergan', 'pyribenzamine', 50 to 100 mg. administered orally or by subcutaneous or intramuscular injection is an average dose, but in some cases this may prove inadequate and as much as 300 to 400 mg., given in divided doses four-hourly, will be required daily. 'Benadryl' given in half the above dose is an equivalent amount. In all cases, rapid, marked reactions leading to drowsiness must be watched for, and patients who drive cars and motor cycles should be warned to be careful. Histamine preparations for children in the form of the elixirs are available. 'Anthisan elixir', 10 to 50 mg. thrice daily, depending upon the age of the child, is a suitable dose.

BACTERICIDES

'Vioform', a quinoline derivative containing iodochlorhydroxyquinoline—41 per cent. of iodine and 12 per cent. of chlorine—in the form of a greyish-yellow powder, has been found useful in treating impetigo, sycosis (folliculitis) barbæ, impetiginized dermatitis, and other conditions in which there is a low-grade coccal skin infection producing superficial irritation, erythema or seborrhœic features. 'Vioform' can be used in the form of a cream or an ointment. The cream, which has a drying water-miscible base, is generally indicated in moist or exudative conditions, whilst the ointment has a greasy base and is suitable for cases presenting crusting lesions.

'Quinolor' ointment has a similar effect, but sometimes the patients complain that it stings their skin. It was most effective in the treatment of many cases of impetigo during the 1939-45 war.

FUNGICIDES

The recognition of the presence and extent of the tinea capitis, and the isolation of infected children, have been facilitated by the examination of the scalp in a dark room using ultra-violet light through Wood's filter. The revelation that the child is suffering from infection by *Microsporum audouini* or *Microsporum canis*, can now be determined with greater speed and accuracy by culture methods. The *Microsporum audouini* infection will probably respond only to X-ray epilation, whereas *Microsporum canis* has an apparently reasonable chance of being treated successfully with a fungicidal ointment.

In cases of tinea capitis, fungicidal ointments have proved successful in the treatment when the *Microsporum canis* is the causative organism. The realization that it is essential to bring the fungicidal ointments as near as possible to the roots of the hair, has encouraged the use of ointment bases which will facilitate contact between the fungus and the drug. The best preparations at the moment for the treatment of ringworm of the scalp are probably blends of salicylic acid and vanishing cream, or salicylic acid and benzoic ointment (Whitfield). The scalp must be washed well every

other day, and epilation with forceps, or the application of a piece of adhesive tape over the affected area, followed by quick removal with the hairs adhering to the plaster, may be necessary later. The production of an artificial kerion by rubbing in salt, crude coal tar ointment, or the frequent application of blister agents is occasionally used for an isolated lesion. This procedure is not suitable for multiple lesions as the ensuing sepsis would delay the time when X-ray therapy, which is nearly always necessary, can be given.

Thallium acetate systemic therapy is still practicable provided the child can be not only accurately weighed and the correct dose given but also very carefully watched during and after the administration of the drug. Vomiting of part of the drug followed by a repeat administration of the same dose may lead to poisoning.

DDT, LETHANE, AND BENZYL BENZOATE PREPARATIONS

The 1939-45 war revealed the extent of lice and scabies among the poorer quarters of large towns. Disorganized civilian life resulting in overcrowding, evacuation and air-raid shelter existence contributed to its spread. Since the use of such preparations as DDT, 'lethane', and benzyl benzoate, the incidence of patients suffering from a mixture of insect parasite infestation and secondary coccal infection has diminished considerably. As a result there are now fewer cases of secondary infection with pyogenic cocci, and less impetigo, erythema and pyoderma. The important points today are to keep the possibility of such infestation in mind in most cases in which itching is a feature, and to avoid prolonged or too vigorous use of sulphur ointment.

THE PSYCHOGENIC FACTOR

The advances that have been made by psychiatrists over the last thirty years have helped us to understand more fully the reaction of the skin to various psychogenic factors. The work of O'Donovan (1927), Klaber and Wittkower (1939) and MacKenna (1944) shows the tremendous importance of combining time-honoured treatments of skin disorders and psychotherapy. That the emotions influence the skin has been known for some time, but the assessment of the importance of psychological factors in initiating and maintaining skin diseases is difficult. It is of interest, for example, that herpes simplex—a vesicular virus infection—may be initiated by emotional tension. This does not mean that herpes simplex is a psychogenic disorder, but rather that the emotional state somehow influences the balance between the virus and the cells in which it lives and so produces—to use the current expression—the 'trigger factor'. Eczema of some types is activated by anxiety, and in other instances nervous tension and pruritus induce scratching and perpetuation of an eruption which in the first instance may have been a contact dermatitis. By this method, a man could 'scratch himself out of the Services' or scratch for himself a lump sum or pension

in compensation. Pruritus ani and vulvæ are often psychogenic symptoms superimposed on a dermatitis medicamentosa; for example, sensitivity to benzocaine or other local anæsthetic ointments. Carefully taken histories in many cases of chronic urticaria, rosacea, psoriasis, seborrhœic dermatitis, acne vulgaris and endogenous eczema have revealed a significant influence of the psychogenic factor (Wittkower, 1949). These disorders have all responded to commonsense and the general practitioner's advice combined with appropriate local and systemic therapy. Certain cases, however, require prolonged rest, special psychotherapy, such as narcosis, analysis, abreaction, and careful guidance and therapy by trained and experienced psychologists.

HORMONE THERAPY

Cortisone and ACTH.—Research in the etiology and treatment of rheumatic disorders and psoriasis arthropathica, culminating in the work of Hench and others, has led to the trial of cortisone and the adrenocorticotrophic hormone (ACTH) in the treatment of a number of unrelated skin affections, with considerable success. Unfortunately, although we are able to relieve disorders such as psoriasis, polyarteritis nodosa, exfoliative dermatitis, pemphigus vulgaris, disseminated lupus erythematosus and rosacea, we now know that the improvement is often only temporary and, even with adequate dosage, may not be maintained. ACTH is given intramuscularly, and stimulates the production of cortisone by the suprarenal cortex. Cortisone, which is also given intramuscularly, acts directly on the tissues, and thus takes the part of the function of a normal suprarenal gland. The shortage of these drugs and the necessity of a maintenance dose has led to a further example of the 'doctor's dilemma'.

Œstrogens and androgens.—Observations made after the administration of œstrogens to women at the climacteric and adolescent girls suffering from seborrhœa, acne vulgaris and seborrhœic dermatitis, have revealed the tremendous influence of hormones upon the skin (Barber, 1949). In certain cases the overactivity of the sebaceous glands has been diminished by the use of œstrogens administered by intramuscular injection or by mouth. When the ratio of androgens to œstrogens becomes increased, overactivity of the sebaceous glands results. A tendency to acne and hirsutism occurs when testosterone proprionate or methyl testosterone has been administered in large doses to menopausal women suffering from metrorrhagia.

When the loss of hair on the vertex of certain men causes great anxiety, the use of œstrogens by local inunction or systemically may be justified. It has encouraged the growth of hair in a certain number of cases. It is very important to keep on the alert for signs of endocrine imbalance which may aggravate the anxiety state, such as lassitude, impotence and enlargement of the breasts.

Thyroid extract.—Chronic ulceration on the legs of fat people should suggest the possibility of myxœdema, and this condition should also be

considered when the skin is very dry, with loss of hair in the temporo-parietal regions and the outer third of the eyebrows. A secondary type of anæmia may also be present. Thyroid extract may be beneficial in such cases. On the other hand, it is wise to be on the lookout for thyrotoxicosis in patients who have severe sweating of the hands and feet.

METABOLIC DISORDERS

Impaired metabolism of carbohydrates, possibly because of changes in the blood sugar level, renders the skin less resistant to staphylococcal and yeast infections and chemical irritants. It is well known that glycosuria may perpetuate symptoms such as pruritus vulvæ. The original condition may be due to an infection by monilia, but its response to treatment with suitable paints is discouraged by glycosuria and scratching, and the application of too many irritating drugs. Certain eruptions, such as seborrhœic dermatitis, acne vulgaris and sycosis, have been favourably influenced by the restriction of carbohydrates. Cure of these cases can only be maintained by the continued teamwork of the general practitioner, physician, pathologist and dermatologist.

VITAMINS

Studies of the effect of large doses of vitamin A on those with a congenitally dry skin, icthyosis, and Darier's disease, have shown that some improvement may occur, and this empirical treatment is well worth a trial (Leitner, 1951). The fact that in most capsules vitamin A is generally combined with vitamin D does not matter. Many acneiform eruptions are reduced by generous doses of vitamins A and C. Cases of furunculosis and pyoderma are also helped either by a diet of fresh fruit, salad and milk or by the use of concentrated vitamin preparations.

Greater knowledge of the control of the vascular supply of the skin has enabled us to assess which patients are likely to benefit from the use of vitamins. Thus, many cases of erythrocyanosis, chilblains, dryness of the finger-tips, cheilitis and angular stomatitis have been helped by the use of the whole or part of the vitamin B complex and vitamin K. 'Priscol', a more recent peripheral vasodilator comprising benzyl-imidazoline-hydrochloride, has a similar effect and has been found well worth a trial in resistant cases of erythrocyanosis and chilblains.

The wonderful advances initiated in 1943 by Dowling and Prosser Thomas in London, and Charpy of France, have led to a disappearance from our clinics of lupus mutilans. In general, one may try the effect of large doses of synthetic vitamin D_2 (calciferol), and later augment this with the older caustic and ultra-violet light therapy. In certain cases a course of streptomycin and PAS may be required. A generous blood supply is needed to bring the calcium and vitamin D_2 to the infected area. Fibrosis around the lesions hinders this so that local erythema-producing therapy is often still

required. In addition, this brings an adequate dose of streptomycin and PAS to the area, and may reduce the tendency to form streptomycin- and PAS-resistant strains.

CONTACT AND INDUSTRIAL DERMATITIS

Demonstrations by Sulzberger and Wise (1931) have shown that it is the epidermis and not the cutis which is the site of the primary lesion in contact dermatitis. Eruptions apparently due to an external irritant are becoming manageable as knowledge of irritants of the skin increases. In addition to the scratch and intradermal methods of testing the skin, patch testing has enabled us to remove the possible source of irritation from the patient (Hellier, 1950; Harley, 1950; Wigley, 1950).

A small portion or suitable dilution of the suspected irritant is placed on a piece of lint and applied directly to the epidermis, usually on the upper arm or back, and covered with a square of adhesive tape. A second piece of lint, but without the irritant, is used as a control on a corresponding surface. These are left *in situ* for twenty-four to forty-eight hours, and a circumscribed area of inflammation, varying from erythema to vesiculation or even necrosis where the allergen is severe, denotes a positive reaction to the substance. The test patch should not be used when the eruption is acute and widespread.

Carefully taken histories of patients suffering from eczematous eruptions of the skin often distinguish a constitutionally sensitive skin from one in which there is a simple trauma or a specific sensitiveness to one or more external irritants. They are particularly important in industry and the home, where paraffins and soap substitutes may remove not only the protective greasy layer but destroy the acid antibacterial mantle of the epidermis. Employees in occupations with a skin hazard should be carefully selected and the suitable ones allowed to try hardening their skin by working for short periods only, in contact with the hazard. Others should adopt precautions such as the use of gloves, aprons, adequate covering of machinery, and specially adapted barrier creams. The success of the treatment of these conditions must be followed by measures to prevent a relapse after a cure. The chief tragedy at the moment is that so little is being done to protect the skin of the hands of the busy housewife and mother.

RADIATION THERAPY

The utilization of rays, in particular those produced by the *alpha*, *beta* and *gamma* radiations, has had a tremendous value in skin disorders. X-ray therapy has enabled us to relieve the symptoms and shorten the duration of illnesses such as acne vulgaris, neurodermatitis, psoriasis, sycosis barbæ, sycosis nuchæ, fungus infections and mycosis fungoides.

In more recent years, it has been found that ultra-violet light is not only useful in inhibiting the growth of organisms, as in impetigo, and stimulating the production of vitamin D_2 in cases of lupus vulgaris, but in some uncertain way leads to relief of symptoms in chronic (constitutional atopic) flexural eczema. This benefit was really noticed by accident when many such

chronic patients were treated in Scandinavian clinics by ultra-violet light, which had become redundant as the result of the remarkable success of vitamin D_2 therapy in lupus vulgaris (Hellerstrom, personal note).

Thorium X, which is a solid substance prepared in the form of an alcoholic solution, varnish or ointment, can be applied locally to the affected parts, and has helped many cases of psoriasis, alopecia areata and capillary nævi (port wine stains).

CONCLUSION

Limitation of space makes it impossible to enumerate all the advances made in recent years. The new cannot always replace the old. An old local treatment which has become popular again is the use of 3 per cent. formalin in water, for ten minutes daily for one week only. This reduces sweating, which is often associated with tinea pedis. The 3 per cent. formalin in water treatment can then be followed by the use of fungicidal paints, powders and acid ointments. Thomson (1943) has pointed out the value of this treatment, combined with curettage, for multiple plantar warts.

Future research will be directed towards the elucidation of the biochemical aspect of skin disease, such as the mechanism of eczema and blister formation, and the interrelationship of hormones, allergy and immunity. The effect of psychogenic influences over the peripheral response of the skin also requires further study. Another line of investigation employing electron microscopy, for the study of collagen and elastic tissue in various disorders, may be promising. Only when more is known of the causative influences at work in various dermatoses will further fields of therapy be opened. In general, it is still most important to maintain a constant lookout for aggravation and spread of a skin disease as the result of local excessive or misguided therapy.

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ADVANCES IN ORTHOPÆDICS

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In the space of a short review it is obviously impossible to refer to many recent contributions to orthopædic practice which might justly be regarded as representing a definite extension of the growing edge of knowledge. I have therefore selected from the material available, five contemporary topics which in my own judgment are especially deserving of commentary.

RECONSTRUCTIVE SURGERY OF JOINTS

For the treatment of disabilities resulting from serious damage to joints, whether by disease or injury, orthopædic surgeons have had at their disposal two contrasting types of operation. In the first place, the joint may be regarded as beyond repair and thus best treated by its deliberate destruction —the operation of *arthrodesis*. Alternatively, an attempt may be made to restore a measure of useful function by the reconstructive procedures commonly designated as *pseudarthrosis* or *arthroplasty*. In recent years striking innovations in the technique of both these types of procedure have been introduced. In arthrodesis of the hip joint, the older techniques were liable to be followed by a high proportion of failures to achieve solid fusion. In the two types of arthodesis devised by Brittain (1948)—the original ischio-femoral arthrodesis by graft, and the V-type, combining graft and nail—the experienced surgeon has a method both precise and safe whereby rapid fixation of a painful deformed hip can be ensured in the great majority of cases. This is a particular boon in patients suffering from monarticular arthritis of the hip joint.

In the field of joint reconstruction it is useful to draw a distinction between the operations of pseudarthrosis and arthroplasty. The essentials of a *pseudarthrosis*—a procedure applicable mainly to cases of bony ankylosis—are a free excision of bone with the creation of a substantial gap, and the avoidance of any attempt to remodel the articular surfaces. The resulting nearthrosis is intentionally relatively insecure, and in a weight-bearing joint a walking appliance may be needed for a time, or even indefinitely. This type of crude joint reconstruction has its place in the mitigation of the grave crippling of bilateral ankylosis of the hip joints in spondylose rhizomyelique. Its usefulness was established beyond all doubt by the late G. R. Girdlestone (1945), and the special technique devised since by Batchelor (1948) constitutes a notable addition to our repertoire. In *arthroplasty* proper, the aim is to retain a close approximation of congruent articular surfaces, permitting a free range of movement with stability.

This demands a conservative resection of bone in ankyloses, and the interposition of material which will prevent fusion occurring between the new articular surfaces before they acquire a fibrous or cartilaginous covering. In the past, muscle, various types of 'foreign body' membranes, and fascia have been used for this purpose.

Nylon arthroplasty of the knee joint.—The operation of arthroplasty of the knee has found little favour among British orthopædic surgeons, despite the somewhat remarkable results achieved by the great Italian surgeon Vittorio Putti in the earlier years following the 1914-18 war. The operation was also practised with considerable success by Willis Campbell and Albee in the United States. In contradistinction to Putti, who reshaped the articular ends of the femur and tibia in accordance with their old conformation, Campbell constructed a unicondylar knee joint, and Albee used a 'tongue and groove' approximation of the femur and tibia. It is noteworthy that many of the successful operations in the practice of these surgeons were performed on knee joints which had fused rapidly after an attack of gonorrhœal arthritis, and which presented a state of complete bony ankylosis unaccompanied by the adverse factors of long-standing muscle wasting and widespread bone atrophy.

For many years the need has been realized for an arthroplasty technique which can be applied to the ankylosed or seriously disorganized knee joints of the victims of rheumatoid arthritis, a disease in which the results of arthroplasty with the traditional interposition of fascia lata have been most disappointing.

Kuhns and Potter of Boston (1951) have recently reported on the greatly improved results observed in 33 knee-joint arthroplasties in which nylon sheeting was used as a covering for the lower end of the femur. Fifteen of the operations were done for bony ankylosis—rheumatoid arthritis (14 cases), and suppurative arthritis (1 case); the remainder were knee joints seriously damaged by rheumatoid or osteoarthritic changes but retaining some degree of painful movement. In all cases the arthroplasty was of the unicondylar type and the after-treatment followed the routine adopted by the earlier pioneers in this field.

Kuhns and Potter attribute the range of comfortable motion which these knee joints have continued to exhibit, to the durability of the nylon membrane. This is obviously a technical advance which deserves to be tried out on a large scale.

Acrylic resin prostheses in the reconstruction of joints.—The increasing use of acrylic resin prostheses as substitutes for damaged articular surfaces, or as a means of filling in extensive gaps after the local resection of primary malignant tumours of bone, has opened a new and fascinating chapter in the reconstructive surgery of the locomotor system. It has been fully established, both by animal experiment and by observations on the human subject, that such plastic foreign bodies do not excite any harmful tissue reaction. The great majority of the operations involving the use of acrylic prostheses have so far been carried out on the *hip joint*. In this field the

brothers Jean and Robert Judet (1951) of Paris have been the pioneers. They were the first to devise and to insert a plastic femoral head as part of the technique of arthroplasty of the hip joint. During the past six years they have operated on some 500 patients, and have recently presented a careful survey of the functional and economic results in 400 cases. Their operations have been carried out for three main groups of hip joint disabilities: (1) chronic arthritis—the largest group—in which good or excellent results were obtained in two-thirds of the cases; (2) fractures of the neck of the femur—either recent fractures or ununited fractures, in which the results were equally encouraging; and (3) old congenital luxations of the hip in which the mechanical difficulties were more formidable owing to the need for extensive remodelling of the socket before the hip could be reduced. Nevertheless, in their view the operation has fully justified itself in this type of hip joint disability.

The *Judet operation* is now being practised on a large scale in France (D'Aubigné and Lance, 1949); it is popular in Belgium (Verbrugge, 1949; Massa, 1951), and already shows signs of competing with the Smith-Petersen vitallium cup arthroplasty in the United States (MacAusland, 1951). The number of operations performed in Great Britain is steadily growing and the procedure seems likely to be in vogue for some years to come. There appears to be no doubt that in osteoarthritis of the hip joint in the elderly, and still more in recent intracapsular fractures of the femoral neck in the aged, it has outstanding advantages over rival methods of treatment. Whether the acrylic resin heads inserted into the hip joints of younger patients for many differing types of mechanical defects of this major articulation will stand up to long years of wear and tear, remains to be seen.

The use of plastic prostheses after extensive bone resection, either for massive innocent tumours or for sarcomas, is already established as a notable contribution to surgical technique. In malignant bone tumours in the upper limb the cosmetic result alone may be of profound psychological comfort during the short survival period vouchsafed to many such patients.

THE BONE BANK

It is only during the last few years that homogeneous bone, preserved under conditions of cold storage, has been freely used in preference to autogenous bone when relatively massive transplants are needed. As might be expected, the practice derives from the United States, the home of refrigeration and more especially of that modern invention the 'deep freeze'. Recent experimental work has shown that the refrigerated homogeneous graft is incorporated in the host bone as completely as autogenous bone, although the pace of the 'take' is somewhat slower (Walsh, 1947). A bone bank is now regarded as an essential part of the armamentarium of all large clinics in the United States in which bone-grafting operations are regularly practised. Such banks receive their deposits from bone removed under strict

aseptic conditions, e.g. ribs from thoracic operations, and bone from fresh amputations. Certain precautions are, of course, necessary. The Wassermann test in the donor must be negative, but he need not belong to the same blood group as the recipient. A number of reports are now available from North American sources which show that the clinical results of the use of stored bone are eminently satisfactory (Bush, 1947; Reynolds and Oliver, 1949; Weaver, 1949; LeCocq, LeCocq and Anderson, 1950). The whole subject has been comprehensively surveyed by Wilson (1951) in a study based both on experimental work and on the results of 248 bone-graft operations carried out at the Hospital for Special Surgery, New York. Wilson concludes that the results as regards 'healing' of these refrigerated grafts are comparable with those previously obtained from fresh autogenous grafts. He advises, however, that stored grafts should be used within a year of their deposit in the bank. He emphasizes the great and obvious advantages of having abundant bone on hand when large amounts are needed, as in spinal fusion operations for scoliosis, or in operations for non-union of fractures in the major long bones. Bone banks are being set up in other countries, and already reports of successful series of homogeneous bone-graft operations are appearing in European surgical periodicals (Herbert, 1951).

INTERNAL FIXATION OF FRACTURES

The Küntscher nail.—During the 1939-45 war, Küntscher (1940) of Kiel began to practise the internal fixation of fractures of the shaft of long bones by means of an intramedullary nail; a method which in other countries had been abandoned after a short trial owing to its adverse effect on union. Küntscher's original technique, which was based on small incisions for the introduction of his special nail and repeated skiagraphic checks, was soon widely followed in Germany, and was enthusiastically adopted by the distinguished fracture surgeon Lorenz Böhler (1948) of Vienna. At first limited to treatment of recent fractures, its use was extended to cases of delayed union and established non-union. Nails were constructed to fit all the major long bones. The technique of blind nailing was inherently difficult, and after the method had been tested in Great Britain—the home of the non-touch technique—it was clear that the nail could be more easily and precisely introduced under the direct control of vision. Further experience has shown that the method is not as widely applicable in the fixation of fractures as was at first assumed (Watson-Jones *et al.*, 1950). Its limitations are now fully appreciated but, nevertheless, it remains the outstanding modern technical advance in the operative treatment of fractures. The method is particularly suitable in fractures of the shaft of the femur, and more especially in those of the upper third. It can be used with safety in pathological fractures of this bone due to Paget's disease, or even due to secondary malignant deposits; and it is often a convenient method of

controlling an ununited fracture in combination with a bone graft. Furthermore, it has no rival as a method of internal fixation in the operation of deliberate shortening of the femur as a means of leg equalization.

MECHANICAL CONTROL OF BONE GROWTH

One of the most distressing problems which has long confronted the orthopædic surgeon, is the treatment of gross discrepancy in the length of the lower limbs. When growth has finished, unilateral shortening can in theory be remedied, either by lengthening the short leg or by shortening the normal leg. In practice both these procedures long ago found a place in the repertoire of the orthopædic surgeon, and particularly the operation of leg lengthening by the technique introduced by Le Roy Abbott for the tibia and fibula (1927), and by Putti for the femur (1921). These operations, which are both difficult and hazardous, have been practised systematically by only a few surgeons. During the growth period, an obvious method of abolishing or reducing discrepancies in length was to interfere with the epiphysial growth discs in the region of the knee in the sound leg. This was the rationale of the operation of complete epiphysial ablation described by Phemister in 1933, and which has been used extensively in children with unilateral shortening due to poliomyelitis. In the approach to this problem the difficulties have lain not in the technique of the operation, but in the choice of the right time for its performance. This has involved considerations such as a study of the family height, and a search for data by which the amount of shortening likely to occur in a poliomyelitic limb could be predicted at an early stage (Stinchfield, Reidy and Barr, 1949). What seemed to be needed was a controlled method of attack on the growing epiphysis which did not involve the final cessation of its function. Such a method has been evolved by Blount and Clarke (1949) of Milwaukee. Temporary complete arrest of growth in length at the knee is achieved by the insertion of staples which penetrate the end of the bone above and below the growth disc. The effect of stapling can be restricted to one side of the growth disc, and thus angular deformity such as knock knee can be gradually corrected. After removal of the staples, epiphysial growth is resumed, usually at the normal rate.

It will be some years before the practical results of stapling in the control of bone growth are available, but the method seems to open a vista of opportunities for the early correction of deformity due to irregular epiphysial activity, as well as its application in the equalization of the length of the lower limbs.

THE CAUSE OF CONGENITAL DEFORMITIES

Interest has recently been reawakened in the classical problem of the etiology of congenital deformities, by the remarkable experimental observations of Duraiswami (1950). Murk Jansen (1867-1935), one of the out-

standing international leaders of orthopædics during the period between the two world wars, argued long and eloquently in support of the view that all congenital deformities were the result of abnormal infolding of the amnion; but at the same time he invoked as a cause of stunting of growth in the embryo, a mysterious humoral factor which he described as maternal 'fatigue'. It has since been demonstrated by animal experiments that certain gross maternal deficiencies in diet may determine skeletal deformities in the offspring, and the relation of rubella contracted by a woman early in pregnancy to the appearance of congenital anomalies in her child appears to be well established. Duraiswami has been able to produce in the chick embryo, by the injection of insulin in the yolk, a range of different skeletal abnormalities depending upon the date and intensity of the injection. Insulin appears to have a powerful effect on ossification, e.g., a general skeletal condition comparable to osteogenesis imperfecta with spontaneous fracture can be induced by injecting the egg on the fourth day. Other deformities produced in this manner have been abnormalities of the claws and beak, and dislocation of the hips.

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ADVANCES IN ANÆSTHESIA

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In the interests of non-specialist readers this short review will be a general presentation of the subject, omitting recondite details. Some recent technical developments will be discussed mainly in respect to their suitability for adoption by part-time anæsthetists, especially those who combine an anæsthetic appointment with general practice.

GENERAL PRACTITIONER ANÆSTHETISTS

First, however, it may be appropriate to consider the present situation of those general medical practitioners who act as anæsthetists from choice or exigency, and to define the scope and standard of their service. The extent to which general practitioners may engage in anæsthetic work is largely determined by geographical factors. Thus, in country places, doctors must include the administration of anæsthetics among several semi-specialized duties expected of them, whereas in most urban areas opportunities to do so have been dwindling for a long time.

Since the inception of the National Health Service, changes in the staffing of many hospitals have temporarily widened the gap in the academic and technical standards of surgeons and anæsthetists serving in them. A surplus of trained surgeons has ensured full establishments of consultants in all hospitals, large or small, whilst a shortage of trained anæsthetists has necessitated the retention of personnel largely self-taught and insufficiently experienced in modern methods.

For years most general practitioners giving anæsthetics in hospital or elsewhere have adhered to the simplest inhalational methods. This was wise so long as operations were inextensive and too few to provide the anæsthetist with such experience as might encourage him to improve his technique. Naturally, in those circumstances, the safety of the patient had to be the primary, if not the only, criterion in the selection and management of the anæsthetic. Nowadays, however, the increasing range of surgery, even in small hospitals, demands that progress should not be hindered for lack of improved methods of anæsthesia ; it is the right of surgeons and patients that good operating conditions should be provided. This is possible with a general practitioner anæsthetic service if those concerned are purposely trained for the work, are given adequate status, and get regular weekly practice to ensure maintenance of proper standards. The latter can hardly be achieved if too many seek to share the anæsthetic duties and thus reduce the amount and worth of the experience for each individually. For efficiency, anæsthesia in general practitioner hospitals should be entrusted to the

smallest number that can regularly and punctually cover the planned operating sessions. In the average small hospital with only one operating theatre a staff of two general practitioners specializing in anæsthetics should suffice, even during holiday periods.

I implied earlier that the safest anæsthetic is not necessarily the best; poor operating conditions and a high incidence of postoperative morbidity may well be the price paid for immediate safety, which in any case is fundamentally related more to the administrator than to a particular drug or method. Modern techniques should therefore not be considered as entirely outside the scope of general practitioners who have the ability and time to master them and can keep in regular practice. It is unlikely that they will be called upon to anæsthetize patients undergoing neurosurgical or thoracic operations. Nevertheless, the transthoracic approach to the viscera of the upper abdomen is becoming common enough, and general practitioner anæsthetists may be expected to undertake with increasing frequency the appropriate anæsthesia for such cases. To do so properly they must understand clearly the significant modifications of respiratory and circulatory physiology produced by newer anæsthetic drugs and methods, and be skilled in their management.

INHALATIONAL ANÆSTHESIA

Ether and chloroform have long been the standby of the medical practitioner called upon to give anæsthetics occasionally. Despite their reputation, effective anæsthesia such as may satisfy the surgeon's need for relaxation is relatively difficult to obtain with these older but potent drugs, besides which their reported simplicity and safety are questionable. The general practitioner in regular hospital work can and must do better than perpetuate outmoded methods of the past. Realizing the shortcomings of these, he may have tried to apply some of the refinements practised by specialists in anæsthetics. In his progress he may already have proved for himself the greater power and flexibility of the inhalational agents when administered from modern apparatus; he may even have ventured on the use of endotracheal tubes and closed anæsthesia with absorption of carbon dioxide.

Tracheal intubation is a worthwhile accomplishment for the general practitioner anæsthetist. Although opportunities to employ the technique may be infrequent, proper instruction and practice in atraumatic intubation are still necessary because of its value in certain emergencies. Of the latter, perhaps the most serious problem is the case of acute intestinal obstruction, a condition in which a copious reflux of fluid from the stomach may occur during induction of anæsthesia or while operation is in progress, and cause death by drowning or asphyxia. To avoid disaster in such circumstances gastric lavage before, and tracheal intubation after, induction of anæsthesia are essential measures. The order indicated for carrying out these precautions should be followed rigidly.

Having acquired some skill in intubation the anæsthetist must not abuse the method by applying it to all and sundry patients for, despite its many advantages, intubation may cause trauma to the air passages and the vocal cords. These complications, which vary from immediate bleeding to post-traumatic effects such as septal adhesions and granulomas of the cords, are usually of minor significance, although their signs and symptoms often appear disproportionate, especially in the opinion of the patient. They are more common after blind naso-tracheal intubation than after passage of the tube through the mouth and between the cords under direct vision; the latter route should be considered the standard one, except for operation within the mouth, when the tube can be kept out of the surgeon's way only by passing it through the nose.

The clear airway which a tracheal tube, carefully chosen as to length and calibre, provides, and the quiet unobtrusive breathing associated with absorption of carbon dioxide from the circulating anæsthetic mixture, are two outstanding improvements in inhalational anæsthesia. By means of them the scope of volatile agents has been extended much beyond the limits possible with 'rag and bottle' methods. Immediate safety and relative freedom from postanæsthetic morbidity are additional features which justify the adoption of the newer techniques even by general practitioners. The latter may be assured there is nothing mysterious in standard apparatus used for the administration of anæsthetic gases in the modern way; the working principles are simple, and flexible control of the level of anæsthesia is readily acquired. Mechanization, although contributing notably to greater efficiency and safety, cannot, however, guarantee these qualities, and does not permit any relaxation of vigilance in the observation and care of unconscious patients.

Improvement and simplification of anæsthetic procedures have gone on steadily for twenty years or more; progress has been accelerated by the introduction of intravenous barbiturates and specific muscular relaxants, particularly the latter. Between them, the natural desire of patients for a speedy and pleasant transition to unconsciousness, and of surgeons for the best possible operating facilities, may now readily be satisfied by novices. Anæsthesia has been made deceptively easy, and thereby potentially dangerous, in the hands of the inexpert. The older methods have some value in the training of anæsthetists, although this alone does not warrant their perpetual retention in clinical practice. There are fundamental differences in the mode of action and effects of the old and new methods. Whereas the former produce what amounts to a pathological state, usually reversible, the latter cause marked derangement of circulatory and respiratory function, but with little cellular intoxication. Thus curariform drugs or local anæsthetics in conjunction with basal narcotics, such as barbiturates or pethidine, do not interfere with the vitality of cells as do ether, chloroform or cyclopropane in doses necessary to produce comparable effects.

INTRAVENOUS ANÆSTHESIA

The question therefore arises, should the new agents and techniques be used by the part-time anæsthetist? In regard to intravenous anæsthesia, popular demand is difficult to resist, and the general practitioner need not do so provided he sets out to make himself proficient in the method and fully understands the attendant risks. The need for oxygen during barbiturate anæsthesia, the dangers of intra-arterial and extra-venous injections of a sclerosing fluid such as thiopentone, the frequency of laryngeal spasm, and the marked limitations of these drugs in producing adequate anæsthesia, must be realized. In domiciliary work a small cylinder of oxygen and simple apparatus for its administration should be part of the equipment whenever and wherever an intravenous anæsthetic is given. Pulmonary ventilation and good oxygenation are of much greater value than the injection of doubtful antidotes. It is important also that records be kept of the exact sites of intravenous injections, because of the possibility of legal action following trauma associated with the method.

MUSCULAR RELAXANTS

Sooner or later a general practitioner anæsthetist may find it necessary to use specific relaxants, if only to comply with the wishes of his surgical colleagues. He ought to anticipate such an event by seeking opportunities to see relaxants in use before attempting to employ them himself. Better still, he should have practical experience under tuition because, as he will quickly learn, the combination of curarization and basal narcosis involves principles and standards in management which differ greatly from those governing general anæsthesia, and these differences must be thoroughly understood before the new responsibility is undertaken.

Although a number of reliable relaxants are available, the original *d-tubocurarine chloride* ('tubarine') is still the standard by which the others are judged; its effectiveness and general suitability have not yet been excelled. Tubarine paralyses myoneural junctions, causing flaccidity of muscles, including the intercostals and sometimes the diaphragm. This extreme interference with respiratory activity calls for special care in the form of artificial pulmonary ventilation by the anæsthetist. Obviously curarization must be limited so far as possible to the period during which relaxation is needed and no longer. The question of giving more tubarine depends upon the progress of the operation and on an assessment of its duration. In a case in which paralysis has not lasted quite long enough, any further relaxation of muscles should be obtained by simply deepening the narcosis. This is preferable to giving additional tubarine at a late stage and having paralysis continue for a time postoperatively. If by any chance this should happen, intermittent pulmonary inflation must be carried on until spontaneous breathing is adequate. Detoxication of tubarine can be accelerated if necessary by intravenous injection of prostigmin (1.0 mg.), and atropine (0.6 mg.),

with repetition of the prostigmin, once or twice until the desired effect is produced. It is unlikely that the anæsthetist who is content to use tubarine in doses just sufficient to produce satisfactory muscular relaxation—usually within the range 10 to 25 mg. in divided dosage—will ever have need to resort to antidotes. This somewhat conservative use of tubarine combines effectiveness with a reasonable degree of safety, and should therefore be the method for the less experienced individual.

Neither tubarine nor any of its substitutes can block painful stimuli, and therefore patients must be under basal narcosis or general anæsthesia. The latter may be kept on a light plane so that toxic effects from the narcotic factor in the technique are minimal. Like spinal block, specific muscular relaxants have made general anæsthesia in its long-accepted form unnecessary. *Basal narcosis*, which must include an analgesic as well as a hypnotic component, is the relatively non-toxic substitute for general anæsthesia that may now supplement curarization or regional nerve block. Much investigation is being done at present of various drugs as possible basal narcotics for continuous intravenous administration. Barbiturates have been tried but because of their lack of analgesic power when given in low concentration are being superseded by pethidine.

Control of light narcosis in conjunction with curarization may present some problems to the inexperienced anæsthetist; a uniform plane between consciousness and deep anæsthesia is sometimes difficult to maintain. Occasionally nitrous oxide and oxygen may be sufficient, but this mixture has only a narrow effective margin. The addition of pethidine or a small quantity of ether, trichlorethylene, chloroform or cyclopropane provides an easily stabilized level of narcosis. At the same time, full oxygenation must be maintained by means of passive pulmonary inflation to compensate for the reduced or absent tidal exchange which accompanies peripheral respiratory paralysis. Failure to do so will result in a lowering of oxygen tension and impedance of carbon dioxide in the tissues which may lead to serious circulatory depression. Quite often, during periods of apnœa, a patient's colour and general appearance may remain deceptively good as a result of diffusion of oxygen into the bronchioles and alveoli, but respiratory function should not be allowed to continue inactivated, except when the surgical procedure may be temporarily benefited by quiescence of the lung, as in intrathoracic operations.

CONTROLLED HYPOTENSION

Another matter of considerable interest to surgeons and anæsthetists is the purposeful induction of vascular hypotension as a means of reducing bleeding during surgery. Loss of blood can endanger a patient's life, whilst bleeding, even small in amount, may affect operative precision and the end-result. Planned interference with circulatory function is only justifiable, however, when competent management can be ensured. No matter how

desirable ischæmic conditions may be, the specialized hypotensive techniques should only be carried out by experts, or alternatively, very circumspectly by those who appreciate fully the physiological changes involved and the ways and means of controlling them.

It is unlikely that the general practitioner anæsthetist will seek to practise either of the earlier methods of inducing hypotension, namely, total sympathetic block or arteriotomy, but he may consider the possibility of using *ganglionic blockade* for the same purpose. The last method is simple, as the hypotensive drug is introduced intravenously in one or more doses according to requirements. The bromides of pentamethonium and hexamethonium paralyse autonomic ganglia and cause generalized vasodilatation. This in itself does not always produce a useful fall of blood pressure because the vasodilatation which occurs may be offset by an increase in cardiac rate and output.

The determining factor in reducing flow-rate, and therefore loss of blood, is the *posture of the patient*. By suitable positioning, the field of operation may be raised above the general level of the patient's body and venous drainage aided. If, as is likely, there is pooling of blood in dependent parts, particularly the legs, the venous return to the heart will be reduced, cardiac output will fall and blood pressure assume a low level. An apparently critical state is thus produced, but this differs significantly from the circulatory depression which accompanies prolonged deep general anæsthesia in that it is quickly reversible and much less dangerous. Safe management of the hypotensive state includes good oxygenation, the patient's respiration being assisted if necessary, systematic recording of blood pressure and pulse rate, and immediate corrective action if untoward signs appear. The development of cardiac arrhythmia is an indication of coronary insufficiency and can usually be eliminated by the elevation of one or both legs. If such a measure is unsuccessful, as it may be if applied too late, a pressor drug must be injected intravenously at once. For this purpose, desoxyephedrine ('methedrine'), in a 15 to 20 mg. dose, is useful; it inhibits amine oxidase and so allows the concentration of adrenaline in the blood to rise, with consequent vasoconstriction, augmentation of cardiac rate and force, and a quick return of circulatory efficiency.

CONCLUSION

The foregoing details may well deter the less experienced from venturing on the methods discussed; but outstanding in what appear to be overcomplicated and even risky features of modern anæsthetic procedures are a marked reduction in over-all toxicity and a much higher degree of reversibility. This is progress, but those responsible for its consolidation must go carefully and dispassionately if they would avoid disrepute for themselves and the new ideas they sponsor.

ADVANCES IN ENDOCRINOLOGY

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ENDOCRINOLOGY has developed very rapidly in the past thirty years. Many factors have contributed to this development, including the isolation, identification and preparation of many therapeutic agents, improvement in the methods of assaying various hormones in the blood and urine, and crucial physiological and biochemical experiments. With the therapeutic agents and laboratory aids that have become available it has been possible to test old hypotheses and develop new ones, as well as to differentiate and describe more accurately various clinical syndromes.

This article will deal primarily with clinical advances in endocrinology, and will refer to physiological and biochemical contributions primarily from the point of view of their bearing on the interpretation of clinical phenomena. The glands of internal secretion are so interrelated that it is difficult to discuss one without frequent reference to others, but for the sake of simplicity each gland will be dealt with separately.

THE PITUITARY

The pituitary consists of an anterior, an intermediate, and a posterior lobe. The anterior lobe is the largest and most important from an endocrine point of view. No clear-cut endocrine function has definitely been established for the intermediate lobe. The posterior lobe is concerned primarily with water metabolism and the contraction of smooth muscle.

THE ANTERIOR LOBE

The anterior lobe of the pituitary produces materials which influence other glands of internal secretion, and these other glands produce hormones which modify pituitary function. Pituitary function appears to be initiated by the hypothalamus. The failure to demonstrate definite nervous pathways from the hypothalamus to the anterior pituitary suggests that the hypothalamic stimulation is mediated by humoral factors. Hypothalamic function is in turn modified by other glands of internal secretion. The evidence available indicates that the anterior lobe of the pituitary is a complex gland of internal secretion with multiple functions, which appear to be mediated through the following hormones: (1) the growth hormone; (2) the thyrotrophic hormone; (3) the parathyrotrophic hormone (?); (4) the adrenocorticotrophic hormone (ACTH); (5) the follicle-stimulating hormone; (6) the luteinizing hormone; and (7) the lactogenic or luteotrophic hormone. Purified preparations have been prepared of the growth hormone, the thyrotrophic hormone (TSH), the adrenocorticotrophic hormone, the

follicle-stimulating hormone (FSH), and the lactogenic hormone. Intensive work with these purified preparations will undoubtedly yield much valuable information concerning the mechanism of their action.

The actions of the various hormones are so interrelated that the effects of the administration of a single purified hormone may not produce all of the effects which occur biologically unless it is supplemented by other hormones. A good example of this fact is the follicle-stimulating hormone which in the ovary causes primary development of Graafian follicles, but will not induce ovulation unless supplemented by the luteinizing hormone, satisfactory preparations of which are not yet available, except for chorionic gonadotrophin, which contains other materials.

All of the pituitary hormones which have been isolated up to the present time are protein in nature and have rather complex molecules of fairly high molecular weight. The crude preparations which have been used in the past have resulted in the development of refractoriness after an initial response. This refractoriness appears to be related to the development of an immune reaction rather than to the production of anti-hormones.

THE GROWTH HORMONE

The growth hormone influences the length of the skeleton, affects carbohydrate metabolism, causes retention of nitrogen, and appears to cause combustion of fat. In its influence on the length of the skeleton its effect is similar to that of the thyroid hormone. However, there are certain important differences in the effects of the two hormones, and the growth changes which they induce are probably mediated in different ways.

The growth hormone of the pituitary is the only hormone which will cause gigantism when present in excess before epiphysial closure. An excess of thyroid hormone will not cause this effect, although a deficiency will cause dwarfism, extreme forms of which are seen in untreated cretins. A deficiency of growth hormone in early childhood will also cause dwarfism, but pituitary dwarfs usually have normal intelligence, whereas cretins are defective mentally. The growth hormone is the only one which will cause acromegalic changes when present in excess after epiphysial closure. The growth hormone affects not only the growth of the skeleton but also the growth of all other tissues. This effect is well illustrated by the hypertrophy of heart muscle and the overgrowth of soft tissue in patients with acromegaly.

Commercial preparations of purified growth hormone are just becoming available. They have been tried in a small number of pituitary dwarfs, and the results up to the present time are very disappointing, in spite of the fact that definite growth has been induced in lower animals. The reason for this difference in effect is not clear.

Growth hormone produces an important effect on carbohydrate metabolism. When given to the dog for a short period of time it produces permanent diabetes, which is presumably the result of interference with the utilization of carbohydrate. The islands of Langerhans in an effort to keep

up with the increased demand for insulin become exhausted and atrophy, and are replaced by scar tissue. The influence of growth hormone on carbohydrate metabolism is different from that of the adrenocorticotrophic hormone, which stimulates the adrenals to produce a Compound E- or Compound F-like material, which in turn causes conversion of protein to carbohydrate.

THE THYROTROPHIC HORMONE (TSH)

It has been suggested that the thyrotrophic hormone may influence thyroid function in one of two ways:—

(1) By causing release of colloid which stimulates the acinar cells to increased activity.

(2) By stimulating the cells of the acini directly to increased activity.

Pituitary stimulation is necessary for normal thyroid function. An excess of thyrotrophic hormone causes hyperthyroidism, and a deficiency causes hypothyroidism. Hyperthyroidism, secondary to hyperpituitarism, is sometimes seen in patients with acromegaly, who often have a goitre, exophthalmos, a high basal metabolism, tachycardia, increased perspiration, and all the other characteristic signs of exophthalmic goitre. Hypothyroidism, secondary to hypopituitarism, is seen in patients with chromophobe adenomas and Simmonds' disease who have a partial or complete loss of all functions of the anterior lobe.

Overproduction of thyrotrophic hormone, mediated through the hypothalamus, is generally considered to be the cause of overactivity of the thyroid in patients with exophthalmic goitre. It has been possible in some patients to cure exophthalmic goitre by irradiation of the pituitary. The following changes have been noted during the administration of the thyrotrophic hormone in man:—

(1) Increase in the severity of toxic goitre, whether of the exophthalmic goitre or nodular goitre type.

(2) Production of a syndrome resembling exophthalmic goitre in patients who have a normal level of metabolism before administration of the substance. The only change characteristic of exophthalmic goitre which has not been produced by thyrotrophic hormone is exophthalmos, and this has been produced in some experimental animals. Some observers, however, believe that the exophthalmos of exophthalmic goitre is produced by some substance other than thyrotrophic hormone.

(3) Increase in basal metabolism in patients with hypothyroidism who have some thyroid tissue capable of functioning.

(4) Absence of increase in basal metabolism in patients with complete hypothyroidism and no thyroid tissue capable of functioning.

The administration of thyrotrophic hormone has been used to determine whether hypothyroidism is primary and the result of some change in the thyroid itself, or secondary and the result of lack of adequate pituitary stimulation. This test may lead to false conclusions because some patients with normal levels of metabolism do not respond to thyrotrophic hormone, possibly because they have an inherent immunity before the administration is begun.

Most observations up to the present time have been made with relatively impure preparations of thyrotrophic hormone, and it is very important that they be repeated with purified products. It will be interesting to observe whether or not the percentage of patients who are initially refractory, and the percentage of those who develop refractoriness during administration of the hormone, are as high as with the cruder materials.

There are probably two types of hyperthyroidism just as there are two types of hypothyroidism; a primary type which originates from some disturbance in the thyroid itself, and a secondary type which is the result of excessive stimulation from the pituitary.

THE PARATHYROTROPHIC HORMONE

A parathyrotrophic hormone has been postulated but the evidence is inadequate. The concentration of serum calcium is sometimes increased in patients with acromegaly, and abnormal depositions of calcium are often seen in this disease. This problem deserves more careful study.

THE ADRENOCORTICOTROPHIC HORMONE (ACTH)

It has been known for many years that there is a close relationship between the anterior lobe of the pituitary and the adrenals. In 1924, Evans reported that the injection of anterior pituitary extracts into rats produced hypertrophy of the adrenal cortex. In 1926, Smith reported that hypophysectomy produced atrophy of the adrenal cortex in animals.

The adrenocorticotrophic hormone (ACTH) was isolated from extracts of the anterior pituitary in relatively impure form by Collip in 1933. In 1943 it was isolated in purer form by Li, using sheep pituitaries and a salt fractionation method, and by Sayers and his associates, using iso-electric precipitation and hog pituitaries. In the past few years purer and more potent forms of ACTH have been prepared. This material stimulates all the functions of the adrenal cortex, although it is still uncertain whether there is a single adrenocorticotrophic hormone which stimulates all functions of the adrenal cortex, or several, each one of which is related to a single function of the cortex.

The adrenocorticotrophic hormone is several times as effective when given intravenously as when given intramuscularly, and it is possible that all hormones of the anterior pituitary produce their maximum effect only when given directly into the blood stream. The action of ACTH may be prolonged by administering it in propylene glycol.

The effects of the adrenocorticotrophic hormone are so closely related to those of cortisone, and so intimately bound up with the functions of the adrenal cortex, that it has seemed best to discuss both together (page 434).

THE FOLLICLE-STIMULATING AND LUTEINIZING HORMONES

The anterior lobe of the pituitary produces gonadotrophic hormones which are closely related to the functions of the sex glands. Follicle-stimulating

hormone causes development of Graafian follicles in the ovary, and stimulates the seminiferous tubules in the testis. Luteinizing hormone causes luteinization of the developing follicles and is probably responsible for ovulation; in the testis it stimulates the interstitial cells to produce androgen.

Preparations of follicle-stimulating hormone in relatively pure form are about to become available on a commercial basis. Their therapeutic efficacy has still to be determined. Most of the preparations contain a small amount of luteinizing hormone, but not as much as older products. With the pituitary gonadotrophins previously available it has been possible to induce ovulation in a few women with anovulatory menstrual cycles. The material has not proved to be of much value in the treatment of infertility in the male. A purified preparation of follicle-stimulating hormone in order to be effective in the treatment of infertility in the female would probably have to be combined with luteinizing hormone.

There is a delicate balance between the anterior lobe of the pituitary and the gonads. The gonads are stimulated by pituitary gonadotrophins, and the pituitary is inhibited by androgen and œstrogen produced respectively by the testes and the ovaries.

THE LACTOGENIC HORMONE

It has been suggested that the main function of the lactogenic hormone is to stimulate secretion of milk after growth of the breasts has already been stimulated by œstrogen. Œstrogen, however, does not stimulate breast growth in the absence of the pituitary. It would appear that lactogenic hormone or some other material from the pituitary, as well as œstrogen, is involved in breast growth. The evidence available indicates that growth of the breast is a complex phenomenon and is dependent upon inherited factors, lactogenic hormone, œstrogen, and perhaps progesterone. The exact rôle played by all of these factors is still to be determined.

OTHER PITUITARY HORMONES

A diabetogenic hormone, a ketogenic hormone, and a pancreatotrophic hormone were, until a few years ago, thought to be produced by the anterior lobe of the pituitary. The evidence available at the present time appears to indicate that the pituitary influences carbohydrate metabolism through the growth hormone and through the adrenocorticotrophic hormone. The ketogenic effect appears to be exerted by the growth hormone. The presence of a pancreatotrophic hormone which was supposed to be responsible for the development of the islands of Langerhans has not been established.

The exact number of hormones produced by the anterior lobe of the pituitary must still remain somewhat in doubt. The problem has been somewhat simplified in recent years but much more work needs to be done, particularly on the interrelation of effects of pituitary hormones. The administration of large doses of one hormone may inhibit production of all

hormones by the anterior lobe. For example, when ACTH is administered in large doses, it appears to inhibit production of thyrotrophic hormone. In this way it has been possible to induce temporary remissions in a small series of patients with exophthalmic goitre.

It appears to be possible to induce inhibition of any gland of internal secretion by administering large doses of the product which it normally produces. Administration of large doses of desiccated thyroid inhibits the normal thyroid; administration of large doses of cortisone inhibits all functions of the normal adrenal cortex; and administration of large doses of testosterone inhibits both functions of the testis. Inhibition of function is thought to be the result of pituitary inhibition induced by thyroid, cortisone, and testosterone.

THE POSTERIOR LOBE

The posterior lobe produces material which has antidiuretic, pressor and oxytocic properties. Abel suggested that one substance was responsible for all of these effects. However, two active factors were extracted in a fairly pure form several years ago by Kamm and Stehle, to which they gave the names 'pitressin' and 'pitocin'.

Pitressin is the pressor and antidiuretic material and produces the following effects:—

(1) In man, a brief fall in pulse rate, oxygen consumption and cardiac output, followed by a more prolonged rise, presumably as the result of an effect on coronary circulation.

(2) An increase in respiratory rate interspersed with periods of apnœa in unanæsthetized animals.

(3) A marked antidiuretic effect lasting for a period of several hours in patients with diabetes insipidus or in those who had previously ingested water. This change is thought to be the result of increased reabsorption of water by certain cells in the tubule of the kidney.

(4) Stimulation of the musculature of the intestine.

Pitocin is the oxytocic factor which causes contraction of the uterus.

Both pitressin and pitocin are said to cause hyperglycæmia and to act as antagonists to insulin. Commercial pituitrin contains both pressor and oxytocic substances but is standardized for its oxytocic activity only. Posterior pituitary extract is also reported to produce the following effects: (1) a decrease in the concentration of fat in serum in man; (2) production of gastric ulcers and marked anæmia when injected into rabbits.

Diseases involving the posterior pituitary gland are rare. The most common is diabetes insipidus, which fortunately is rarely encountered in patients with pituitary disturbances. When the disease is present, a careful search should always be made for a tumour in the hypothalamic area or a pituitary tumour encroaching on the hypothalamus. Diabetes insipidus can be controlled satisfactorily by administering pitressin tannate in oil, intramuscularly two to three times per week. In rare instances patients are encountered who have excessive secretion of a pitressin-like material which causes transient attacks of retention of water.

THE THYROID

Most of the evidence available indicates that the thyroid produces only one hormone, which is thyroxine in chemical combination. The hormone is produced in the cells of the acini and stored in the colloid. From the colloid it is released according to the needs of the body. The thyroid gland in its natural state produces thyroxine in the lævorotatory form, which is much more active than the dextrorotatory form.

More is known about the thyroid than any other gland of internal secretion. It has been shown that there are 10 to 14 mg. of thyroid hormone in the body of a normal man outside of the thyroid in terms of racemic thyroxine, and the thyroid elaborates its hormone in terms of this material at the rate of 0.33 mg. daily. The hormone appears to be secreted in the form of thyroglobulin or a polypeptide, and serves as a catalyst in all the cells of the body. Like most hormones it influences the functions of all tissues. A great deal of information has been obtained in recent years concerning thyroid function, and particularly on the interrelation of the anterior lobe of the pituitary and the thyroid. The most important clinical advance has been in the treatment of *toxic goitre*. The introduction of anti-thyroid drugs and radioactive iodine has completely revolutionized the treatment of this disorder.

Anti-thyroid drugs have been used in two ways: (1) to prepare patients for operation; (2) to treat the disease medically. With anti-thyroid drugs it is possible to eliminate the thyrotoxicosis completely before the patient is subjected to any surgical procedure. The result is that the mortality from subtotal thyroidectomy for toxic goitre is now as low as the mortality from subtotal thyroidectomy for non-toxic nodular goitre. In leading thyroid clinics it has dropped from 1 per cent. to about 0.1 per cent.

The usual procedure is to give propylthiouracil or some other suitable material until the basal metabolism becomes normal. Compound solution of iodine or some other suitable preparation of iodine is then given for a few days preoperatively to promote storage of colloid and reduce the vascularity of the gland. During the short period of iodine administration propylthiouracil may either be continued or its administration discontinued. In many clinics it is stopped when iodine is begun so that there will be no risk of a reaction to the drug in the immediate postoperative period.

In some clinics anti-thyroid drugs are used routinely in the preoperative management of all patients with toxic goitre. In other clinics they are used only in patients who have toxic goitre in moderately severe or severe form, and not in patients who have the disease in mild form. The results appear to be about the same, regardless of which form of treatment is employed.

The use of *radioactive iodine* represents an important advance. It is effective by mouth, and severe reactions do not occur from its use as they often do from anti-thyroid drugs. Radioactive iodine will induce a permanent remission in as large a percentage of patients with exophthalmic goitre as a subtotal thyroidectomy. There is no way at the present time of determining the effective dose before treatment is started, and in some instances it may be necessary to give as many as five doses before a cure is produced. An interval of six to eight weeks is usually allowed to elapse

between each two doses. The size of the initial dose varies in different clinics but is commonly between 5 and 10 millicuries. *Nodular goitre* with hyperthyroidism can be controlled by radioactive iodine, but much larger doses are required than in the treatment of exophthalmic goitre.

In most leading thyroid clinics there is agreement concerning the treatment of toxic goitre, and the consensus may be summarized as follows:—

(1) In most patients with toxic goitre the best form of treatment at the present time appears to be a subtotal thyroidectomy after adequate preoperative preparation with propylthiouracil, iodine, and a high caloric diet.

(2) The use of anti-thyroid drugs and radioactive iodine for medical management should be restricted for the present time to patients over forty-five years of age and to patients of any age who present poor operative risks. In older patients it may be used routinely because the dangers involved are slight. It is generally felt that for medical management radioactive iodine possesses many advantages over propylthiouracil. The likelihood of producing a permanent remission is much greater and there is no danger of a toxic reaction.

(3) It is still too early to be certain whether or not radioactive iodine induces the development of carcinoma of the thyroid. The evidence available appears to indicate that it does not do so in man, but several more years must elapse before any definite conclusions can be drawn concerning this problem. It is mainly for this reason that it is felt that radioactive iodine should not be used routinely in the management of exophthalmic goitre until more data are available.

(4) Patients, with nodular goitre and hyperthyroidism should have a subtotal thyroidectomy after adequate preparation, regardless of the age of the patient, unless they present poor operative risks.

(5) The percentage of permanent remissions with anti-thyroid drugs is too low and the incidence of reactions from them is too high to warrant their routine use in the medical management of toxic goitre.

It is generally agreed that *exophthalmic goitre* is caused by a disturbance of a hypothalamic-pituitary-thyroid complex, and the administration of radioactive iodine and anti-thyroid drugs represents attacks on the thyroid rather than on the cause of the disease. Several years ago we were able to produce a remission in one-third of a small series of patients with toxic goitre by irradiation of the pituitary. The percentage of remissions was too low to warrant the routine use of this form of therapy.

Some improvement has been made in the management of *carcinoma of the thyroid*. The importance of early detection has been stressed and the treatment has been somewhat improved. About 13 per cent. of cancers of the thyroid take up enough radioactive iodine to control the disease. The uptake of radioactive iodine may be greatly increased in about 50 per cent. of the remainder by the use of thyrotrophic hormone, or by a surgical or functional thyroidectomy (radioactive iodine) which increases the output of thyrotrophic hormone by the pituitary. A few spectacular cures of metastatic cancer of the thyroid with radioactive iodine have been reported.

THE PARATHYROIDS

The parathyroid glands produce a single hormone which is concerned with calcium and phosphorus metabolism. The exact nature of the hormone is unknown, but active preparations have been extracted from the gland. An excess of parathyroid hormone causes the concentration of calcium in

serum to rise to abnormally high levels, and if not checked may result in death. Calcium is withdrawn from bone and excreted in the urine. As calcium is withdrawn, osteoporosis, bone cysts and sometimes benign giant cell tumours of bone develop. Decalcification of the teeth does not occur. When a deficiency of parathyroid hormone is present, the concentration of calcium in serum drops to abnormally low levels and tetany is produced, with numbness and tingling of the extremities, carpopedal spasms, increased electrical excitability of nerve and muscle, and eventually convulsions and death. Bilateral cataracts are an end-result of untreated tetany.

The concentration of phosphorus in serum in parathyroid disease varies inversely with the concentration of calcium. Thus, in hyperparathyroidism it is low, and in hypoparathyroidism it is high. Parathyroid tetany is most commonly encountered following a subtotal thyroidectomy but in rare instances it is spontaneous in nature. It does not occur in more than 1 per cent. of patients undergoing a subtotal thyroidectomy in the hands of competent surgeons.

The concentration of calcium in serum can be maintained at normal levels in patients with parathyroid tetany by the oral administration of calcium salts supplemented by the administration of large doses of vitamin D (50,000 to 150,000 U.S.P. units daily) or by the administration of an irradiated ergosterol, 'dihydrotachysterol'. Dihydrotachysterol is probably the most effective method of treatment, but it must be used with caution. Its effect is slow and cumulative, and if given in too large doses will cause the serum calcium to rise to dangerously high levels. The concentration of calcium in serum must be observed at frequent intervals to make sure that the proper dose is given. When parathyroid tetany is far advanced, it may have to be controlled initially by the intravenous administration of a suitable calcium salt. Extracts containing the parathyroid hormone are not suitable for prolonged management because refractoriness to them appears to develop. With adequate treatment the serum calcium can be maintained within normal limits. Patients can be kept free of symptoms and free from the danger of developing cataracts. Cataracts develop only in untreated or inadequately treated patients.

THE ADRENALS

Great advances have been made in our knowledge of adrenal function, particularly as a result of the observations with ACTH and cortisone. Each adrenal gland has two functioning parts, a cortex and a medulla. The combined weight of the glands in adult life is about 28 grammes. Their importance is out of all proportion to their size.

The medulla.—The main function of the medulla is to produce an adrenaline-like substance which affects the function of the sympathetic nervous system. Its administration stimulates the production of adrenocorticotrophic hormone by the pituitary. Tumours of the adrenal medulla phæochromocytomas) may develop which produce an excess of adrenaline

and are characterized by transient attacks of hypertension, palpitation, tachycardia, cyanosis, and pallor of the extremities. There is no clear-cut clinical syndrome which is correlated with a deficient production of adrenaline. This substance is not essential for life, but its administration may be a life-saving measure in patients with foreign protein reactions.

The cortex.—The adrenal cortex has three main functions which until recently have been thought to be related to three different types of steroid hormones:—

(1) A desoxycorticosterone-like material which affects sodium and potassium metabolism and blood pressure.

(2) A cortisone- or Compound F-like material which influences carbohydrate metabolism (gluconeogenesis).

(3) Androgenic material which is related to the anabolism of protein, to the growth of hair in the pubic, axillary and other regions, to the maturation of bone, and to other functions.

There is still uncertainty concerning the number of hormones actually produced by the adrenal cortex. Twenty-eight different steroid compounds have been isolated from this gland, but there are many reasons for believing that most of them represent degradation products of the true hormones. There are three main possibilities at the present time which may be summarized as follows:—

(1) There may be three different steroid hormones related to the three main functions of the gland.

(2) There may be one key hormone which influences both electrolyte metabolism and carbohydrate metabolism with the androgenic function controlled by a separate hormone.

(3) There may be one key hormone which influences all three functions of the adrenal cortex.

According to the third hypothesis, desoxycorticosterone, cortisone, Compound F, and perhaps certain androgens, may represent degradation products of the key substance. By perfusing the adrenals with desoxycorticosterone, cortisone has been produced, and in a similar manner what has been thought to be a key substance or a more potent material has been produced by cortisone.

Certain observations are not consistent with the idea of a single adrenocorticotrophic hormone. Masculinizing tumours are sometimes observed in which the only alteration in function is excessive production of androgen without any change in the electrolyte or carbohydrate metabolism. In rare instances patients with diabetes mellitus have been reported who have developed Addison's disease, in which the only change in the function of the adrenal cortex was a diminished production of the electrolyte factor.

THE CORTEX

The most significant developments in our knowledge of adrenal cortical function have come about in the last few years through the use of ACTH

and cortisone. The effects of these two substances are so closely related that they will be discussed together.

Cortisone, or Compound E, was isolated from beef adrenal glands in 1936 by Mason, Myers and Kendall. It is present in very small quantities in the gland, and it has been suggested that Compound F, which can be recovered in larger quantities, is the hormone which is normally present rather than Compound E. The chemical name for cortisone is 11-dehydro-17-hydroxycorticosterone, whereas Compound F is 17-hydroxycorticosterone. The administration of cortisone represents substitution treatment with a single compound, whereas the administration of ACTH stimulates all three functions of the adrenal cortex.

The most important impetus for the clinical application of ACTH and cortisone came in 1949 when Hench, Kendall *et al.* reported the dramatic results of the administration of cortisone to patients with rheumatoid arthritis, acute rheumatic fever and some other conditions. Their work dealt chiefly with cortisone, but it was well known at that time that the administration of ACTH stimulates all of the functions of the adrenal cortex, and it was felt that this material might therefore represent more desirable therapy than the administration of cortisone, which is only one steroid that can be recovered from the gland.

The work of Hench and Kendall was confirmed in many clinics, and their work may be regarded as one of the most important developments in medicine in the past decade. It has stimulated observations which have caused us to modify our notions concerning the nature of many disease states.

The dramatic effects of ACTH and cortisone have focused attention on the general adaptation syndrome of Selye and on the important part which the adrenal cortex plays in health and disease. It has become more and more apparent why the adrenal cortex is so essential for life and why the loss of adrenal cortical function leads to such profound chemical changes in the body.

ACTH AND CORTISONE

Both ACTH and cortisone appear to be effective in the same diseases, although ACTH seems to be more effective in some conditions than cortisone. The administration of ACTH produces the following effects:—

(1) An increase in the retention of sodium, chloride and water.
(2) A decrease in the excretion of sodium, chloride and water.
(3) A variable amount of increase in the concentration of sodium in body fluids.
(4) Increased excretion of potassium.
(5) Decrease in concentration of potassium in body fluids.
(6) Increase in the carbon-dioxide-combining power of the blood.
(7) Gluconeogenesis (conversion of protein to carbohydrate) which may be reflected in an increased excretion of nitrogen in the urine. Marked hyperglycæmia and glycosuria may develop in mild or potential diabetics.
(8) Increased production of androgen which is reflected in an increased excretion of 17-ketosteroids in the urine.
(9) A sense of well-being and some degree of euphoria. In psychotic individuals, actual psychoses may develop.
(10) A variable effect on the blood pressure. In most instances no change occurs

but some increase is occasionally noted.

(11) A decrease in the total number of circulating eosinophils.

(12) Disappearance of fever regardless of the cause.

Whilst cortisone affects primarily carbohydrate metabolism, it does have some influence on sodium and potassium metabolism and does increase the excretion of 17-ketosteroids, possibly through conversion in the body. Retention of sodium, chloride and water with large doses of ACTH may be so great that a generalized anasarca develops.

Administration of large doses of these substances will produce in the aggregate all of the manifestations of Cushing's syndrome, although not all in any one patient. There is some question as to whether or not they produce the characteristic purplish striæ seen in this disorder, but their production is claimed by some observers. If a Cushing-like syndrome develops as a result of the administration of ACTH and cortisone, its manifestations usually disappear when the administration is stopped.

The increase in blood pressure produced by these materials is variable.

ACTH and cortisone produce frank diabetes only in mild or potential diabetics. In patients who have diabetes mellitus the severity of the disease is greatly increased, as shown by an increase in the insulin requirement. Diabetes mellitus does not develop in individuals who have a normal insulin-producing mechanism in the pancreas. If diabetes does develop, the carbohydrate metabolism usually returns to normal when the administration of either substance is discontinued.

General therapeutic considerations.—ACTH and cortisone influence favourably many disease states. The nature of the effect is unknown. They probably affect some phase of metabolism which is common to these disorders, particularly the various allergic states. One of the most important effects of both compounds is on collagen tissues. They inhibit fibroblastic proliferation. Two things should be pointed out:—

(1) In certain diseases in which the changes are far advanced, for example, rheumatoid arthritis, the alterations produced by the disease are irreversible and cannot be eliminated.

(2) There is a tendency for a relapse to occur following initial improvement in spite of continuation of treatment.

Certain details of treatment are still to be worked out. It is uncertain whether it is better to give treatment continuously or intermittently, whether it is better to give large initial doses or gradually increasing doses, and whether treatment should be withdrawn gradually or suddenly. Doses of ACTH and cortisone which must be used to produce improvement in most diseases are so large that the effects should be regarded as pharmacodynamic rather than physiological. Patients with Addison's disease who have a complete loss of adrenal cortical function may be maintained with 12.5 to 25.0 mg. of cortisone daily, whereas 100 mg. a day or more may be necessary to maintain improvement in patients with rheumatoid arthritis. Patients with Addison's disease who have no functioning adrenal cortical tissue rarely have

any of the diseases which are reported to be favourably affected by the administration of ACTH and cortisone. Adrenal insufficiency cannot therefore be considered as the cause of most of them. This fact is also consistent with the hypothesis that the effect is pharmacodynamic.

There is no evidence that any disease has been permanently cured by the administration of ACTH or cortisone, although in some instances long periods of remission may follow their administration. These remissions usually occur in diseases which are characterized by remissions and relapses. In most instances a relapse sets in shortly after treatment is discontinued.

In following the course of treatment with ACTH and cortisone it is important to bear the following things in mind:—

(1) The general condition of the patient with special reference to the development of weakness and œdema. Whenever there is any doubt about the ability to tolerate them, their administration should be discontinued.

(2) The concentration of sodium and potassium in serum.

(3) The level of the fasting blood sugar and the excretion of sugar in the urine.

(4) The sedimentation rate.

(5) The eosinophil count. The administration of ACTH or cortisone characteristically produces a decrease in the total number of circulating eosinophils. The reduction in the total number of circulating eosinophils following the administration of ACTH is a fairly reliable index of the functional capacity of the adrenal cortex and has been used preoperatively as a measure of the risk of operation.

Clinical applications.—ACTH and cortisone will produce a beneficial effect which is often dramatic in the following conditions:—

Rheumatoid arthritis and related conditions, including rheumatoid spondylitis, Still's disease and psoriatic arthritis
Acute rheumatic fever
Disseminated lupus erythematosus (early)
Addison's disease (cortisone but not ACTH)
Pneumonia
Asthma (status asthmaticus)
Inflammatory eye diseases
Exfoliative dermatitis
Pemphigus
Panhypopituitarism
Idiopathic hypoglycæmia

In the following conditions the results are encouraging but further observation is necessary:—

Various allergic states, including hay fever, angioneurotic œdema, drug sensitization and serum sickness
Gout
Ulcerative colitis
Regional enteritis
Nephrotic syndrome
Scleroderma (early)
Dermatomyositis
Psoriasis
Periarteritis nodosa (early)

Pulmonary granulomatosis
Alcoholism
Agranulocytosis
Certain forms of anæmia
Burns

Transient beneficial effects have been reported in the following conditions:—
Acute leukæmia (lymphocytic or granulocytic)
Multiple myeloma
Lymphosarcoma
Hodgkin's disease
Chronic lymphatic leukæmia

No clear-cut beneficial effects have been reported in the following disorders:—
Myasthenia gravis
Cushing's syndrome
Amyotrophic lateral sclerosis
Multiple sclerosis
Progressive muscular dystrophy
Progressive muscular atrophy
Congestive heart failure (may be detrimental in some cases, but cases secondary to acute carditis may be benefited through effect of cortisone on inflammatory lesions)
Chronic myelogenous leukæmia
Acute monocytic leukæmia
Glomerulonephritis (exclusive of nephrotic syndrome)
Poliomyelitis
Osteoporosis (may be detrimental?)

Addison's disease.—Cortisone has improved greatly the ability to manage patients with Addison's disease. The best method of treating patients with this disorder at the present time appears to be the combined administration of deoxycortone acetate in the form of pellets, and the oral administration of cortisone. Pellets are usually implanted every six to eight months, the usual dose being 300 mg. (four pellets of 75 mg. each), and cortisone is given every day by mouth in a dose of 12.5 to 25.0 mg. With the combined treatment patients have more strength, gain more weight, are more resistant to intermittent infection, and have fewer crises than with any other form of treatment.

The administration of ACTH in patients with hypoadrenalism is of value in determining whether the deficiency is primary or secondary. If it is secondary to hypopituitarism, ACTH will cause a characteristic adrenal cortical response. If it is the result of destruction of adrenal cortical tissue, ACTH is ineffective.

CONTRAINDICATIONS TO THE USE OF ACTH AND CORTISONE

The administration of ACTH and cortisone appears to be contraindicated in the following conditions: (1) congestive heart failure; (2) chronic nephritis; (3) hypertension; (4) Cushing's syndrome; (5) diabetes mellitus; (6) various psychoses and psychiatric tendencies; (7) hirsutism; (8) immediately preceding or following various surgical procedures, because of inhibition of the development of fibroblasts.

Patients show great variation in their susceptibility to the administration of ACTH and cortisone. Some will develop retention of fluid and electro-

lytes and various types of depression or excitement with as little as 50 to 60 mg. a day, whilst others may not show such changes with doses as large as 250 to 300 mg. a day. Patients who are treated must be watched carefully to detect complications as soon as they develop.

THE PRESENT STATUS OF ACTH AND CORTISONE

The work with ACTH and cortisone represents one of the most important developments in medicine in recent years. It has demonstrated conclusively the very important part which the adrenal cortex plays in body metabolism, and has forced us to reorient our ideas concerning the nature of some clinical phenomena.

As the evidence has accumulated, the attitude toward administration of ACTH and cortisone has become more conservative. It has become more and more apparent that they usually do not cure any disease but merely induce certain chemical changes which hold it temporarily in abeyance. As data become available on long periods of observation, it is evident that the beneficial effects often disappear in spite of continuation of treatment.

The biochemical and physiological advances which have occurred as a result of the observations with ACTH and cortisone appear to be more significant than the therapeutic applications. The observations which have already been made are of great significance, and intensive study will yield results of even greater importance.

THE TESTES

Large doses of androgen, such as 50 mg. of testosterone propionate three times a week by intramuscular injection, will produce inhibition of both testicular functions, and azoospermia will result. Histologically, the testis shows an extreme form of degeneration, but following withdrawal of androgen therapy it gradually recovers and may in the course of seventeen to twenty-four months function better than before androgen therapy was started. This observation is now being applied in the treatment of infertility in males with deficient spermatozoa counts. The results are promising in a small number of patients, but further observations must be made over a much longer period of time before the value of this form of treatment can be determined.

The testicular inhibition which is associated with the administration of large doses of androgen presumably occurs as a result of inhibition of gonadotrophic production by the anterior lobe of the pituitary. In patients with secondary hypogonadism the administration of chorionic gonadotrophin, which stimulates the interstitial cells of the testis, may through an increase in androgen production cause some stimulation of spermatogenesis.

It has been pointed out in the section on the pituitary that testicular and ovarian function are closely related to the gonadotrophic function of this gland. Hyperfunction of the gonads is not common but various types of hypofunction are often observed. Hypogonadism may be primary and the result of a defect in the gonad itself, or secondary and the result of lack of

adequate stimulation by the anterior lobe of the pituitary. The secondary type is more common than the primary type.

In most individuals with hypogonadism both gonadal functions are deficient but they may vary independently of one another. Thus, in the testis there may be a deficient production of androgen and deficient or absent spermatogenesis in the same individual, but it is not uncommon to observe patients with fairly satisfactory production of androgen whose spermatogenic function is very deficient. In rare instances the opposite of this condition is noted, namely, deficient production of androgen with fairly satisfactory spermatogenesis.

These three types of testicular deficiency may occur on a primary or secondary basis, the exact type depending upon the pathology involved. In hypopituitarism the nature of the hypogonadism depends upon whether there is a deficiency of both follicle-stimulating hormone and luteinizing hormone or a deficiency of one with satisfactory production of the other. Similar changes are observed in the ovary. Further intensive study of the physiological alterations involved in various types of menstrual irregularities will yield important results. It has been suggested that the Sertoli cells of the seminiferous tubules produce œstrogen, but the evidence is inadequate.

The androgen produced by the testis is responsible for the development of secondary sex characteristics, including the growth of the genitalia, development of the musculature, growth of hair in the pubic and axillary regions and on various parts of the body, lowering of the pitch of the voice, and skeletal moulding. Production of androgen appears to be responsible for the spurt in growth that occurs at puberty. It is not certain what part androgen production by the adrenal cortex plays in the development of both sexes, but it does appear to have something to do with the growth of pubic and axillary hair and, when present in excess in the female and in young boys, will induce masculinizing changes. The exact form in which androgen is secreted by the interstitial cells of Leydig is not known. Testosterone is the most potent material isolated so far. The sex hormones are general metabolic stimulants which influence the functions of all cells of the body and not merely materials which influence sex function.

On theoretical grounds substitution therapy with sex hormones is indicated in patients with primary hypogonadism, whereas stimulation therapy with various gonadotrophic materials is indicated in secondary hypogonadism. In actual practice the therapeutic attack is limited by the agents available. Substitution treatment with androgens and œstrogens is very effective when they are specifically indicated. Stimulation treatment is not so satisfactory.

The most potent stimulating agent at the present time is chorionic gonadotrophin which is very effective in secondary hypogonadism in the male. It is much less effective in the female. The preparations of pituitary gonadotrophin that have been available have not been very effective in either sex, but they have caused some stimulation of ovarian function and

have induced ovulation in some women with anovulatory menstrual cycles. In most cases of hypogonadism in the female it is necessary to use substitution therapy with œstrogen regardless of whether the gonadal deficiency is primary or secondary in type.

THE OVARIES

Knowledge of ovarian function, and particularly of the hormonal factors involved in normal and abnormal menstruation, has been greatly increased. The ovary produces two hormones, œstrogen and progesterone, and their production is in turn initiated and modified by the two gonadotrophic hormones of the anterior lobe of the pituitary.

Œstrogen is produced by the developing follicle and the corpus luteum, whilst progesterone comes principally from the corpus luteum. Œstrogen influences most functions of the body and plays a major part in the development of the secondary sex characteristics, including growth of the genitalia and breasts, skeletal moulding, characteristic feminine distribution of fat, and emotional changes. It also causes retention of calcium. During the menstrual cycle it causes hyperplasia of the uterine glands and of the vaginal epithelium. Progesterone causes further changes in these structures, and produces tortuosity and proliferation of the uterine arteries. Progesterone is reported to play some part in the growth of acinar tissue in the breast.

The hilus of the ovary contains cells which resemble histologically the androgen-producing cells in the reticular zone of the adrenal cortex. They sometimes undergo hyperplasia or tumour formation and give rise to masculinization.

THE PANCREAS

The number of hormones produced by the pancreas is uncertain. Insulin is produced by the islands of Langerhans and plays an important part in carbohydrate metabolism. It appears to cause conversion of glucose to glycogen, but all phases of its action have not been worked out. The pancreas has also been reported to produce a hormone which increases the level of the blood sugar, but the data are unsatisfactory.

A few years ago Dragstedt reported the isolation of a hormone from the pancreas which he called lipocaic, and which he claimed affected fat metabolism by enabling the liver to transform fat into phospholipid, which is the utilizable form. The exact status of lipocaic is uncertain.

Many hormones besides insulin play an important rôle in carbohydrate metabolism. The important part played by the growth hormone and by ACTH which stimulates the production of a cortisone-like material in the adrenal cortex have already been discussed.

The severity of diabetes mellitus may be greatly reduced by the development of Addison's disease. Exacerbation of diabetes mellitus occurs during the administration of ACTH or cortisone, and diabetes mellitus sometimes develops in patients with acromegaly. The level of the blood sugar must

not be thought of in terms of insulin production alone but also in terms of pituitary and adrenal function. A low concentration of sugar in the fasting blood may indicate overproduction of insulin or inadequate production of ACTH or a cortisone-like material. A high level of sugar in fasting blood may mean either a deficient production of insulin or excessive production of growth hormone, ACTH, or a cortisone-like compound.

GASTRO-INTESTINAL TRACT

Many hormones have been claimed for the gastro-intestinal tract, but the presence of the following six appears to have been established:—

(1) Gastrin, which stimulates the formation of acid by the stomach.

(2) Secretin, which stimulates the output of water and bicarbonate by the pancreas.

(3) Pancreozymin, which increases the concentration of enzymes in pancreatic juice.

(4) Cholecystokinin, which causes the gall-bladder to contract and evacuate.

(5) Enterogastrone, which inhibits the motility of the stomach and the secretion of acid by the stomach in the presence of a 10 per cent. concentration of fat in the small intestine.

(6) Duocrinin, which stimulates Brünner's glands to secrete an alkaline mucilaginous fluid in copious quantities.

Gastrin is formed in the gastric mucosa principally at the pyloric end of the stomach. The other hormones are produced in the mucosa of the upper portion of the small intestine.

OTHER HORMONES

No clear-cut hormonal function has been proven for the pineal gland. Cases of gigantism associated with a tumour of this organ have been reported, but it has not been established that altered function of the pineal gland is the factor responsible.

Various hormones have been ascribed to the liver, kidney and other organs but their exact status is not clear.

SUMMARY

A résumé has been given of the more important developments in endocrinology in the past thirty years. A great deal of progress has been made in the identification, synthesis and purification of hormonal substances which are highly effective therapeutically. Many syndromes associated with hypofunction and hyperfunction of various glands of internal secretion have been clearly defined.

Endocrinology has become established as an exact science but, in spite of the important developments which have occurred, only a beginning has been made. Intensive study during the next thirty years will yield even more significant results.

CURRENT THERAPEUTICS

XLVI.—THE USE OF CORTISONE IN RHEUMATIC DISEASES

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THE work of Hench, Kendall and associates (1949) concerning the effects of cortisone and the pituitary adrenocorticotrophic hormone (ACTH) has been an epochal advance in medical science. Stimulated by their report, there has been much investigation of the many effects of cortisone, related steroids, and of ACTH. Some investigators, including my own research group, have been particularly concerned with the practical aspects of the clinical use of cortisone in the management of patients. This report will serve primarily to summarize the experiences of our research team, and to compare these with pertinent work of other investigators. I gratefully acknowledge the cooperation of the several investigators in my research unit, whose work has made this report possible.

Most physicians are familiar with the chemical structure of cortisone; all practitioners and investigators are fully aware of the many physiological effects of this steroid. The reduction of stiffness, decrease of joint pain and swelling, increase in motion and strength and the improved general health of patients with rheumatic diseases, together with the return to or toward normal of related laboratory changes, are generally referred to as the 'anti-rheumatic effects' of cortisone. In contrast to other substances formerly used as anti-rheumatic agents, the three main attributes of cortisone are: (1) its speed of action; (2) dependability; and (3) the magnitude of its benefit. These remarkable anti-rheumatic effects have raised the hopes of rheumatic patients, and of physicians responsible for their care—both groups anticipating the improved management expected from this steroid.

Adrenocorticotrophic hormone will produce precisely the same anti-rheumatic effects by stimulating the patients' adrenals to produce and/or liberate cortisone (or Compound F). Because this hormone can be used only by intramuscular injection, required two to four times daily, it has far less practical usefulness, except for short periods and in hospitalized patients. Hence, most of our clinical studies have been concerned with different methods of using cortisone. Because of this fact and the recent discussions of ACTH in this journal, attention will be confined to practical considerations of cortisone in rheumatic diseases.

The manner of action of cortisone is unknown. All of the known chemical

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and metabolic effects of cortisone fail to account for its anti-rheumatic effect. The local changes seen when cortisone is instilled directly into the conjunctival sac, or injected into a joint, indicate that the steroid produces beneficial effects directly at the tissue level; and the speed of response, as well as results of recent research (Anderson *et al.*, 1951), suggest that the action is on an enzyme system. Other possibilities include changes in antigen-antibody relationship and alteration in tissue permeability (Seifter *et al.*, 1949). Regardless of how it functions it is clear that to benefit rheumatic disease cortisone must be present in the tissues in greater amounts than are required to offset the cortisone deficiency of Addison's disease. This is one of the factors which makes its clinical use for rheumatic disease more difficult.

PREPARATIONS

Cortisone was originally prepared as small crystals in aqueous suspension for intramuscular injection. Soon it was found advantageous to prepare it as an acetate and this salt was used in aqueous suspension,* 1 ml. containing 25 mg., until it was shown that the steroid was effective when administered orally (Freyberg *et al.*, 1950). During the past year most of our studies have employed cortisone acetate in tablets used orally.

It was not surprising to us to find that this steroid is effective orally, for some other steroids were known to be; but it was surprising to find that the effect is more rapid and shorter in duration when given orally, and that the amount required orally is so little more than the amount needed by injection to produce a comparable effect. When given orally in a single daily dose, our early studies showed that an average of 1.7 times the intramuscular dose was required for similar effect. Soon it was discovered that if divided into two to four doses, the daily oral requirement is no more than 1.2 times the intramuscular dose. Thus, in divided doses the effect was smoother and the drug efficiency greater. It is now commonly supplied in 25 mg. scored tablets so that 12.5 mg., or multiples thereof, can easily be arranged. It is not necessary first to give cortisone acetate intramuscularly before it is used orally, as some physicians have erroneously believed.

The technical and economical advantages of oral cortisone are obvious. There is little variation in effect among patients; the presence, or amount, of gastric HCl and liver disease with even high-grade dysfunction have not altered the absorption or effectiveness of oral cortisone (Freyberg and Stevenson, 1951). Injection abscesses are, of course, obviated. Nausea, vomiting and diarrhœa may prevent dependable effects from oral cortisone. The chief problem relating to the use of cortisone tablets is that the entire responsibility for dosage rests with the patient and, because of misunder-

*Merck & Co., Inc., Rahway, N.J. Kindly supplied in generous amounts for investigation through the courtesy of Drs. J. F. Carlisle and A. Gibson.

standing, carelessness or direct intent, the directions of the physician may not be followed, and this powerful hormone may be abused.

Recently we have studied preparations of cortisone acetate especially prepared for intravenous use. So used, the steroid was effective and usually well tolerated, but the indications to date (studies unfinished) are that with rare exceptions this is an impractical way to administer the drug and that there are no routine advantages when so given.

For use in the eye, a mixture of 1 part of the standard suspension of cortisone acetate in 4 parts normal saline is well tolerated and effective. For intra-articular injection, the suspension prepared for intramuscular use has been successfully employed.

CLINICAL CONSIDERATIONS

The remarkable benefits of cortisone have been observed in therapeutic trials in many different forms of rheumatic disease. In all instances it has been observed that the effects of cortisone are profound so long as the steroid is administered, but that these effects cease soon after its use is discontinued. In illnesses which naturally tend to be of short duration, such as bouts of gouty arthritis and acute rheumatic fever, cortisone can be expected to benefit the patient greatly and, due to the short period of administration required, there is little or no difficulty from undesired physiological action ('side-effects'). However, in a chronic disease, such as rheumatoid arthritis, greater difficulties accompany the use of cortisone, for it is evident that the underlying disease process is not eliminated by use of the steroid, and prolonged, vigorous use may produce serious side-effects. Since the desire for, and the problems of use of, cortisone seem greatest in rheumatoid arthritis, this will be discussed first.

RHEUMATOID ARTHRITIS

The practical questions are: (1) Can cortisone be safely and effectively used for the benefit of patients with rheumatoid arthritis?; and (2) if so, what therapeutic schedule is best? Our experiences over the past two years help to answer these questions. Three possibilities exist for beneficial use of cortisone for chronic rheumatoid arthritis:—

(1) Effect a suppression of the disease by use of cortisone, and sustain the benefits by other means.

(2) Repeated suppressing treatment by use of the steroid in short courses separated by rest periods.

(3) Prolonged use of cortisone as 'maintenance treatment'.

Our abundant experience with the first two possibilities was summarized recently (Freyberg *et al.*, 1951a) and indicates that these are generally unsatisfactory means of managing this chronic rheumatic disease. Various steroids, other than cortisone, including pregnenolone, failed to sustain the benefits of cortisone. As we used it, gold salt was ineffective in sustaining

cortisone effects. This is in agreement with reports of others (Kammerer, Cecil and Robbins, 1951); however, Margolis (1951) has reported that gold salt appeared to sustain the benefits of ACTH. It seems unlikely, but the effect of gold salt may differ in conjunction with these two hormones. Further study is required to determine this.

It was disappointing that in all patients short courses (seven to twenty-one days) of cortisone were always followed by relapse of the disease with the same speed and of the same degree after successive courses, so that no lasting benefit occurred.

Prolonged use of cortisone as 'maintenance treatment' was managed with the suspension injected *intramuscularly* as follows:—

> On the first day, 200 or 300 mg. of cortisone acetate were injected in 100 mg. doses; from the second day on, 100 mg. were injected daily until the desired *partial*, not complete, remission was accomplished—usually in seven to fourteen days; thereafter 100 mg. were injected on alternate days or three times weekly (Monday, Wednesday and Friday). In many patients this maintained the desired effect. In some, 'booster treatment' using 100 mg. daily for seven to ten days, was needed at intervals of thirty or sixty days. When tablets were used, on the first and second days, 50 or 75 mg. were usually given three times, after meals (150 to 225 mg. per day); continuing from the third day, 50 mg. were given after breakfast, 25 mg. after lunch and dinner, daily until the desired effect was obtained, after which 37.5 to 75 mg. were required daily to maintain the effect. Maintenance cortisone was given in divided doses after meals. When the daily total was 37.5 or 75 mg., equal amounts constituted each dose, i.e. 12.5 or 25 mg.; when the total was 62.5 or 50 mg., the divided doses were 25, 25, 12.5 mg., and 25, 12.5, 12.5 mg., respectively. Such maintenance use of oral cortisone was found the most satisfactory.

Our results of such prolonged use of cortisone have been reviewed recently (Freyberg *et al.*, 1951b). Forty-four patients were studied: 25 females, 19 males. Treatment was continued in all, for more than 100 days; in 17, more than 200 days; in 9, more than 300 days; in 4, more than a year. The degree of partial remission sought was sufficient to relieve most of the pain and stiffness, and to improve function so as to rehabilitate the patient substantially. In so doing, clinical and laboratory signs of disease persist, but are considerably reduced.

With such management, good to excellent anti-rheumatic effects were usually maintained *during* administration of the hormone. In only 4 per cent. of trials was long-term use of cortisone stopped because of poor therapeutic effect. In most instances 50 to 75 mg. of cortisone acetate, given orally, was required daily for 'maintenance'. If more than 75 mg. daily were required it was found that complications sooner or later made it impossible or undesirable to continue. The variation in maintenance dose correlated chiefly with the severity of the disease, not with its duration or with the age, size or sex of the patient. In amounts up to 75 mg. daily 'maintenance' cortisone was usually well tolerated, although the longer the treatment, the greater the chance for trouble. Complications were usually readily corrected or controlled. The nature and incidence of complications are shown in table 1.

TABLE 1
COMPLICATIONS OCCURRING DURING MAINTENANCE CORTISONE IN 44 PATIENTS

Type	Incidence					
	Degree				Total	Per cent.
	+	++	+++	++++		
Round face	10	2	1		13	30
Obesity	6	2			8	18
Hirsutism	4				4	9
Acne	2				2	4
Œdema	14	6	2		22	50
Potassium decrease	4					9
Diabetes		1		1	2	4
Irregular menstruation	8				8	32
Menopausal symptoms	5				5	20
Jitteriness, insomnia	9	2			11	25
Excitement	2				2	4
Depression			1		1	2
Tachycardia	12	2	2		16	36
B.P. elevation	11	3			14	32
Telangiectasis	2				2	4
Purpura	3	2			5	11
Hæmorrhage (G-I)				2	2	4
Thrombosis (leg)	2				2	4
Thrombosis (coronary)					0	0
Cardiac decompensation					0	0

Complications predominated in females.
Some abnormalities listed may not be due to cortisone.

We think it significant, but cannot explain the fact, that the incidence and severity of complications were considerably greater among female patients. Prolonged treatment was discontinued in 24 cases; in 18 cases treatment was stopped deliberately in order to study post-cortisone events. In 6 instances (14 per cent.) it was considered necessary to stop cortisone due to diabetes and mental depression (one instance of each), œdema in 2 patients, and massive hæmorrhage into the gastro-intestinal tract in 2 patients. Five of these 6 patients were females.

Just as the benefits *during* treatment were usually gratifying, the difficulties *after* prolonged treatment were very disappointing, both to the patient and physician. These events are summarized in table 2.

Within sixty days, relapse to pre-treatment level had occurred in 84 per cent. of the patients. In many instances relapse started when the daily dose was reduced below 50 or 25 mg. It is considered important that even the patients with early disease relapsed promptly after discontinuance of cortisone. Also relapse occurred as often in those patients treated for 200 to 370 days as in those treated for 100 to 200 days.

As suspected, there was evidence of suppressed adrenal function in many patients, but this recovered within two to six weeks.

A very distressing illness which we call 'post-cortisone withdrawal

syndrome' occurred in 21 per cent. of patients. Again, note that 4 of these 5 patients were females. This syndrome is characterized by severe and disproportionate weakness, stiffness, and fatigue, anorexia, mild hypotension, great discouragement and depression. These patients were miserable; usually they stayed in bed and required assistance for nearly everything. The syndrome always subsided in two to eight weeks but some patients felt more ill then, than before treatment, and volunteered that they did not wish cortisone administered again.

TABLE 2
POST-CORTISONE EVENTS IN 24 CASES

	Number	Per cent.
Continued improved (50 to 75 per cent.), 60 to 190 days	4	16
Relapsed to pre-treatment condition:—		
Within 10 days	6	25
10 to 20 days	8	33
20 to 30 days	4	16
30 to 60 days	2	8
	Total 24	
Includes 2 cases of early disease (6 and 8 months' duration) Includes many cases treated 200 to 370 days		
Adrenocortical insufficiency—temporary ..	10	40
'Withdrawal syndrome'	5 (4 females)	21
Fracture of the hip	2	8
Œdema	3	12
Difficult readjustment to worsened disease	4	16

Whenever possible it is advisable to discontinue cortisone gradually for the metabolic, endocrinological and psychological adjustments are more easily made. Often patients with no special trouble found it very difficult to adjust psychologically to their worsened state after a 'holiday' affected by cortisone.

Based upon these experiences, which are similar to those published by Boland and Headley (1951) and reported by Ward and Slocumb *et al.* (1951), (the only other large groups studied, so far as I am aware) this type of maintenance cortisone treatment appears to be valuable for some, but not practical for all, patients with rheumatoid arthritis. Hence such treatment should not be considered as routine, but should be selected for definite purposes, such as a rapid worsening of the disease, and to facilitate physical treatment and rehabilitation. Further study is required to make cortisone more generally useful in the treatment of rheumatoid arthritis.

Rheumatoid variants.—Rheumatoid spondylitis (Strümpell-Marie, ankylosing spondylitis), 'psoriatic arthritis' and Still's disease (juvenile rheumatoid arthritis) are affected in the same way as, and the problems are similar

to, those of characteristic rheumatoid arthritis. The dosage for children is not determined by the size or age of the patient, but rather by the severity of the disease; usually it approaches or equals the adult dose, and when so used excess hormone effects produce more complications than in adults.

Osteoarthritis.—Boots (1951) has reported good results using cortisone for patients with *malum coxæ senilis*. I, too, have observed increased comfort from cortisone in a few patients with osteoarthritis. It appears to help these patients chiefly or only through affecting analgesia. Realizing the nature of this disease, cortisone would seem to have a very limited place in the management of this form of rheumatism.

Fibrositis.—Several patients with generalized primary fibrositis were found to derive much relief from cortisone while it was used, and showed prompt and complete relapse after it was discontinued. Because of the mild nature of this rheumatic disease and its tendency to chronicity it would seem unwise to consider the use of such a powerful agent as cortisone for treatment.

For painful, stiff ('frozen') shoulder, and for the shoulder-hand syndrome, Steinbrocker and his co-workers (Ehrlich *et al.*, 1951) have reported benefit using cortisone acetate in doses of 100 to 200 mg. daily, for three to six weeks, in conjunction with physical measures, to restore joint motion, not obtained by other forms of treatment.

RHEUMATIC FEVER

Many investigators (Hench *et al.*, 1950; McEwen *et al.*, 1950; Barnes and Smith, 1950; Massel and Warren, 1950) have shown the excellent anti-rheumatic effects of cortisone in patients with rheumatic fever. Within a day or two, signs of illness disappear or improve, and complete suppression of the disease often results within twenty to thirty days. Doses of 200 mg. for two or three days, followed by daily doses of 100 mg. for four to eight weeks, usually accomplish excellent suppression of the disease. If discontinued too soon, rheumatic recurrences develop; reinstitution of treatment again suppresses the disease. Because this rheumatic activity naturally tends to continue for a short time only, it is reasonable to plan treatment with cortisone as needed to suppress the disease until the abnormal processes which characterize the illness subside, after which the patient can be expected to continue in good health, without the steroid. Because of the short period cortisone is usually required, side-effects from the steroid are infrequent or mild.

It is hoped that early and proper use of cortisone during active rheumatic fever may prevent or lessen the valvular and myocardial complications. This seems reasonable, but a longer time of study is required to know if this be true. Also more investigation of their relative merits is required to indicate whether cortisone or salicylates is the treatment of choice in different cases.

OTHER CONDITIONS TREATED WITH CORTISONE

Gouty arthritis.—In some patients with acute gouty arthritis, cortisone acetate, given intramuscularly or orally in quite large doses (200 to 300 mg. daily) for a few days, quickly suppresses the attack. Recurrence is less likely to occur when the steroid is discontinued if colchicine is used at that time, in doses of 0.5 mg. twice daily, for a few days. In some of our patients cortisone has been valueless. We reserve the use of cortisone or ACTH for those gouty patients who fail to be helped by colchicine or who are intolerant of colchicine.

Our experience with cortisone used in patients with *disseminated lupus erythematosus* is similar to that reported by Brunsting, Slocumb and Didcact (1951). There is often a striking relief of symptoms of the disease, and improvement in the patient's well-being. Clinical remissions have resulted in some cases, but in all there is no significant improvement in the tissue or laboratory changes. The steroid effects are temporary only, but prolonged treatment may lengthen life. Side-effects are more apt to occur in the more severely ill patients with involvement of the heart and kidneys.

Cortisone appears to be less beneficial to patients with *periarteritis* and *scleroderma;* further study is required to determine the scope of their usefulness for these maladies.

Non-rheumatic disorders.—Cortisone is known to cause remarkable benefit in adrenal insufficiency, and in some allergic disorders, eye inflammations, some skin diseases, and drug reactions, and it may be useful in some neoplastic diseases, but these diseases are not within the scope of this article.

INTRA-ARTICULAR USE OF CORTISONE AND COMPOUND F (17-HYDROXYCORTICOSTERONE)

The effects of cortisone acetate and compound F acetate* injected directly into affected joints have been studied in many patients with rheumatoid arthritis, and in a few patients with osteoarthritis. Amounts up to 75 mg. of each steroid have been injected into a joint at one time. Administered intra-articularly, both steroids are usually well tolerated and produce considerable relief. In osteoarthritic joints the benefit is chiefly relief of pain; in rheumatoid joints there is reduction of the local inflammation. Our experience (Freyberg *et al.*, 1951a; Stevenson and Freyberg, 1951) corresponds in general to that of Hollander (1951). Compound F is more uniformly beneficial, and its effects are more prolonged than those of cortisone, intra-articularly. Such intra-articular injections, if not required too often, may be of practical value to patients with monarticular arthritis or in those persons disabled by a single diseased joint.

LIMITATIONS OF USEFULNESS

There are several features which limit the clinical usefulness of cortisone.

*Kindly supplied by Merck & Co., Inc., Rahway, N.J.

This steroid has remarkable powers of righting metabolic abnormalities or reversing the pathological physiology of some diseases. But it has not the power to eliminate pathogenic factors; hence it cannot be expected to cure any disease. It has value only during the period of administration, so is temporally limited. It has no reparative value in damaged tissues; hence it cannot be expected to restore deformed arthritic joints, or cardiac valves. The numerous undesired physiological effects, both hormonal and metabolic, may exceed the desired effects of the steroid, so as markedly to limit its clinical usefulness.

GENERAL PRECAUTIONS

The most important safeguard for the patient receiving cortisone is a thorough understanding of the known physiological effects of this steroid by the physician. During the use of the drug the patient should be kept under close surveillance and routine clinical check regarding nervousness, insomnia, excitability, personality change, weight, pulse, blood pressure, œdema and menstrual disorders should be made. Weekly, or biweekly, urine analyses and sedimentation rate determinations are advised, and if abnormalities are found so to indicate, blood sugar and potassium determinations and an electrocardiogram may be helpful.

Tuberculosis is usually made worse by cortisone administration, so that patients with this disease should not receive it. To patients with renal disease, hypertension, diabetes, and active peptic ulcer, cortisone should either not be given, or if used it must be extremely carefully managed. Nervous and psychiatric complications are much more likely to occur in those persons who have had psychic tendencies. We have observed no difficulty in wound healing in patients receiving usual dosage of cortisone.

SUMMARY

Cortisone has potentialities for remarkable benefit in various rheumatic disorders, and it has definite limitations of clinical usefulness. Most of these are discussed in this report.

For acute illnesses the use of cortisone presents relatively little difficulty; it is in chronic disease that the greatest problems are encountered. Many patients with rheumatoid arthritis tolerate well, and are helped by, moderate amounts of cortisone used over a long period of time. But in the large majority of cases after discontinuance of the steroid, even when used for a long time, the disease relapses promptly and severely; some patients have a severe 'withdrawal syndrome' or difficulty in readjusting to the worsened state of the arthritis. These facts detract considerably from its clinical usefulness. There is no evidence that the course of rheumatoid arthritis is *ultimately* altered favourably by prolonged cortisone therapy.

For these reasons cortisone is not considered practical treatment, *routinely*, for rheumatoid arthritis; rather it is carefully selected for a definite purpose, with full realization of its limitations and problems. When corti-

sone is used, trouble must be expected in some patients, and the physician should be prepared to meet this. We now appreciate that one must consider not only what will happen *during* its use, but also what might occur *after* its use is discontinued.

Investigators realize the great potentialities for clinical usefulness of cortisone in rheumatoid arthritis. Never before has such a potent anti-rheumatic substance been available. But for more general clinical use, we need to know better how to use it. Search for the knowledge on which to base a more satisfactory and practical treatment programme is going forward, stimulated by the fact that never before has this search been so hot on the trail of success.

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REVISION CORNER

TENESMUS

TENESMUS may be defined as a painful and frequently recurring urge to defæcate, associated with griping pain and producing but little fæcal result. Accurate diagnosis of the cause of tenesmus may present a difficult clinical problem, and a brief consideration of the physiology of defæcation is a useful preliminary before approaching the clinical features and underlying pathology.

The innervation of the movement of defæcation is governed by two centres: a medullary centre situated in the floor of the fourth ventricle, and a spinal centre in the second, third, and fourth sacral segments. The passage of fæces past the pelvi-rectal junction, filling the rectum, promotes strong peristaltic contraction of the colon accompanied by shortening of the bowel (due to contraction of the longitudinal fibres in the tæniæ coli). At the same time there is a coordinate relaxation of the anal sphincters, which results in defæcation. Diarrhœa is a frequent accompaniment of tenesmus, but it must be remembered that diarrhœa alone will not necessarily cause recurrent and painful desire to defæcate. Pain will occur if there is any upset in the normal reflex control of defæcation; this may arise from direct irritation of the mucosa of the rectum or rectosigmoid region or the termination of the pelvic (parasympathetic) nerves in these areas, or the cause may lie in some interruption to the normal reflex arc with resultant incoordination and spasm of the sphincter muscles.

CAUSAL FACTORS

The following table provides a useful classification of the causes of tenesmus:—

(1) *Acute generalized gastro-intestinal infections*
- (a) Bacillary dysentery
- (b) Salmonella
- (c) Staphylococcal and streptococcal infections
- (d) Typhoid and paratyphoid
- (e) Cholera

(2) *Inflammatory lesions of the colon*
- (a) Amœbic dysentery
- (b) Tuberculosis
- (c) Uræmia
- (d) Ulcerative colitis.

(3) *Chemical poisons*
- (a) Metals—arsenic, mercury and gold
- (d) Purgatives

(4) *Local lesions of the rectum and sigmoid*
- (a) Polypus, adenoma, carcinoma
- (b) Volvulus, intussusception
- (c) Fissure, thrombosed hæmorrhoids
- (d) Diverticulitis

(5) *Pelvic*
- (a) Pelvic abscess, posterior prostatic abscess
- (b) Ischio-rectal and peri-proctal abscess
- (c) Ovarian cyst, ectopic pregnancy

(6) *Disease of the pelvic nerves*
- (a) Tabes—rectal crises
- (b) Neoplastic infiltration

(7) *Allergy*

(8) *Autolytic*
- (a) Gastro-colic fistula
- (b) Gastro-enterostomy

CLINICAL FEATURES

Severe examples of tenesmus are encountered in acute *gastro-intestinal infections*. In this type of infection, the history is typically of sudden onset of severe diarrhœa

accompanied by lower abdominal pain; at first the stools are frequent, copious, and only partly formed or watery. After a few hours there is a progressive reduction in the amount of fæcal material passed, but the frequent desire to defæcate persists, perhaps twice in an hour, and with scarcely any evacuation apart from a little blood and mucus. Clinical examination reveals little that is abnormal apart from lower abdominal tenderness and perhaps a low-grade pyrexia; a careful and detailed history is therefore essential to establish a diagnosis.

The most important group of organisms are, of course, the dysenteric organisms, the infection spreading from one person to another by food contaminated with excreta. *Bacillary dysentery* is often spread by milk, dairy products, and by flies; the illness varies considerably in its severity, so that the possibility of a symptomless carrier must always be considered when one or more members of a family succumbs. Other organisms, including the *Staphylococcus aureus* and occasionally certain strains of hæmolytic streptococcus, may cause a similar acute gastro-enteritis; but this type of infection is encountered as a result of infected ice cream or milk and consequently produces several explosive outbreaks. Recent evidence appears to show that some virus infections may also produce an identical clinical picture.

Similar tenesmus accompanied by diarrhœa also occurs in *ptomaine poisoning;* the differential diagnosis from acute dysentery is difficult, and depends mainly upon the sudden outbreak of vomiting, diarrhœa and prostration in several members of the same family or families, all of whom have recently consumed the same meal. It may be that the sufferers will proffer their own diagnosis by identifying the responsible article of diet—usually meat or a meat preparation. Other bacterial infections which may cause tenesmus include *cholera, typhoid, paratyphoid,* and occasionally *tuberculous enteritis.* Bacteriological examination and culture of the infected stools should be completed as soon as possible in all cases of suspected bacterial infection.

Of the protozoal infections, *amœbic dysentery* is the most important cause of tenesmus. Although in most cases there will be a previous history of acute amœbic dysentery, the disease does occasionally arise as a primary infection in the United Kingdom, and not infrequently in patients who have only recently arrived by air from the tropics. Examination of a *freshly* passed stool is essential, since the diagnosis can be established only by demonstrating *E. histolytica* or its cysts in the warm stool.

Poisoning by certain *heavy metals* excreted in the colon may closely simulate acute gastro-enteritis, and cause severe tenesmus. Not only arsenic, but also mercury and gold must be considered, since both the latter are widely used in therapeutics. When the history suggests metal poisoning, clinical examination may reveal early signs of polyneuritis or dermatitis.

Ulcerative colitis may occasionally present with tenesmus as the dominant symptom; it is surprising how often patients with ulcerative colitis make little complaint of their diarrhœa, but tend to stress the associated pain. Examination of the stools is most helpful, since the fæces in this condition are partly formed but contain considerable amounts of mucus with fresh blood; pus, too, is often visible. Sigmoidoscopy will confirm the diagnosis, showing multiple shallow ulcers extending below the recto-sigmoid junction, some covered with beads of pus and surrounded by reddened, engorged mucosa.

Of the local lesions of the recto-sigmoid region which give rise to tenesmus,

polypus, *adenoma* and *neoplasm* seldom present any diagnostic problem, provided the clinical examination includes proctoscopy as well as a rectal examination. *Volvulus* and occasionally *intussusception* of the lower sigmoid loop may cause painful and frequent defæcation; diarrhœa does not occur in these cases, and the presenting symptoms are severe and constant lower abdominal pain (with colicky pain superimposed), tenesmus, and the passage of very small amounts of *fresh* blood and mucus. It may be possible to palpate a thickening of the bowel in the left iliac fossa. Anal lesions, such as *thrombosed piles* and *anal fissure*, are, of course, often the cause of tenesmus. Lastly *proctitis* must be mentioned; as an isolated lesion it is uncommon, and is more often secondary to pelvic infection such as peri-proctal abscess or diverticulitis with pelvic abscess.

Genito-urinary lesions seldom cause tenesmus, but the symptom does occasionally arise from a posterior *prostatic abscess*, and sometimes as a result of pressure on the rectal wall from an *ovarian tumour* or *ectopic pregnancy*. Disease of the pelvic nerve roots may give rise to tenesmus; the rectal crises of *tabes* are, of course, the classical example. Similar painful crises may occur when there is extensive neoplastic infiltration of the pelvic nerve roots; in such cases the primary tumour is evident on pelvic examination.

In *allergic subjects*, severe diarrhœa, with the passage of fresh blood and mucus in the stools, accompanied by tenesmus may follow the ingestion of some specific food 'allergen'. These patients are usually well aware of the cause of their troubles, and other allergic manifestations (particularly urticaria and occasionally hæmaturia or joint effusions) may be present.

Lastly, mention should be made of two other conditions causing diarrhœa and tenesmus; these symptoms may arise suddenly as a complication of peptic ulcer or following gastro-enterostomy, and this should arouse suspicion of the possible development of *gastro-colic fistula*.

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NOTES AND QUERIES

The Clinical Use of Aminophylline

QUERY.—What is the action of aminophylline given orally, intramuscularly, and intravenously? Are there any indications for its use in heart disease that cannot be met by digitalis, or morphine, or a restricted regimen? I have several asthma patients who find an intramuscular injection gives them relief when adrenaline and various nebulæ have failed, but are deterred by the pain after the injection. Is aminophylline compatible with novocain?

REPLY.—Aminophylline (U.S.P.) is also known as theophylline with ethylenediamine (B.P.), cardophylin, theamin, and euphyllin. The British Pharmacopœia gives aminophylline as a synonym. The ethylenediamine fraction is used chiefly to render the theophylline soluble, but it probably exerts some action in its own right when the combination of the drugs is used to stimulate the respiratory centre. Aminophylline acts as a diuretic chiefly by diminishing tubular reabsorption. It tends to abolish Cheyne-Stokes respiration by its stimulating effect on the respiratory centre. It has a striking although rather short-lived stimulatory effect on the heart muscle, and the coronary flow increases. The balance of evidence is in favour of the view that the increased coronary flow is secondary to the myocardial stimulation, but some observers have reported beneficial effects from its use in the treatment of angina of effort. Aminophylline dilates the bronchi by a direct action, and it is of value in the treatment of asthma refractory to adrenaline, ephedrine and isoprenaline. Its chief drawback is again the short duration of its effects

To produce results with certainty, aminophylline should be given by slow intravenous injection. It is also effective when given intramuscularly, but many patients complain of the pain it produces. There seems to be no reason why it should not be given along with procaine (novocain). A mixture of the drugs gives no precipitate. It is too painful for subcutaneous use. When given orally, absorption is uncertain and gastro-intestinal side-effects are often severe. It is often administered by this route as a diuretic, to prevent attacks of angina of effort, and to diminish the severity of asthmatic attacks in children. Results are uncertain. It may be effective in asthma when given by inhalation as an aerosol.

In heart disease, theophylline with ethylenediamine, when given intravenously, will reduce the venous pressure in cardiac failure and give a rise in cardiac output. Its action is, however, short-lived. It may give dramatic if temporary results in the dying heart, and its effects are more pronounced in degenerative and hypertensive heart disease than in failure due to valvular disorders. It is the only drug of proved value in the treatment of Cheyne-Stokes breathing.

The dose given in the British Pharmacopœia is 0.1 to 0.5 g. (1.5 to 8 grains). The official injection contains 0.25 g. in 10 ml. for intravenous, and 0.5 g. in 2 ml. for intramuscular use.

PROFESSOR E. J. WAYNE, M.D., F.R.C.P.

Sterilization of Syringes

QUERY.—Is ordinary methylated spirit sufficient to store hypodermic syringes in after sterilization or should a pure form of alcohol be used? It is not easy to carry syringes about in one's case in an ideal way as regards sterilization. I wonder if you have any practical hints. For years I have boiled my syringes after each use, dried out with methylated ether and wrapped in fresh cotton-wool, reassembled, and returned to my case. Before using I well rinse out a new needle and syringe with methylated ether. Is there any better method?

REPLY.—Alcohol in a strength of 70 to 75 per cent. (by volume) is a quick and effective disinfectant against vegetative bacteria such as staphylococci and streptococci, but is ineffective against the spores of such organisms as the tetanus and gas-gangrene bacilli. Alcohol above 90 per cent. and below 50 per cent. is a poor disinfectant. The appropriate strength is best obtained by diluting industrial methylated spirit, which corresponds to 90 per cent. alcohol.

Syringes and needles should be *immersed* in the spirit for fifteen to twenty minutes and no attempt should be made to sterilize syringes, particularly the Record type with its numerous crevices, by rinsing (i.e. filling and expelling) with spirit. If a syringe has been used for aspirating pus or other infective material, it should first be thoroughly cleaned and then sterilized by boiling, or, better still, by high pressure steam in a pressure cooker. It may then be stored in 70 per cent. alcohol and rinsed with freshly boiled water before use.

An alternative method for the practitioner who has to give a number of injections of penicillin, streptomycin and the like, on his round is to assemble the syringe and needle after sterilization by heat and place them in a sterile container (a pyrex glass test tube with a small piece of glass tubing to encase the needle and a cotton-wool plug, or a metal or plastic case with lid or top is suitable for the purpose). Enough solution for a single dose is drawn into the syringe. After the injection the plunger is kept firmly 'home', and on withdrawal the needle, still attached to the syringe, is plunged completely into boiling water for ten to twenty seconds. This procedure sterilizes the part that may have become infected, and the assembled syringe and needle can then be replaced in the container ready for the next injection (see Fleming and Ogilvie, *Brit. med. J.*, 1951, **i**, 513). If the syringe is to be used for the injection of different sterile fluids, e.g. insulin followed by penicillin, it should be rinsed with freshly boiled water *after* sterilization of the needle as described above.

PROFESSOR ROBERT CRUICKSHANK, M.D., F.R.C.P.

Malignant Œdema of Malnutrition

QUERY (from a reader in S. Africa).—What is the treatment of malignant œdema of malnutrition? We often see the condition among Zulu infants who have been malnourished since birth. Œdema is usually gross, serum proteins generally much reduced and albumin-globulin ratio reversed. The danger period appears to be the period when the œdema has just subsided, as death often takes place then. Are mercurial diuretics of any use? How can one distinguish between this condition and beriberi, and other conditions in infants giving gross generalized œdema?

REPLY.—The treatment of malignant œdema of malnutrition is a high protein diet with vitamin supplements, particularly of the B group; milk or powdered milk is a convenient source of the protein, and yeast or marmite of the vitamins. The œdema is associated with a lowered osmotic tension of the blood from diminution of plasma protein, with consequent retention of water in the tissues. There is accompanying liver damage with consequent inhibition of plasma albumin synthesis.

Correction of the dietary deficiencies is obviously of primary importance. Mercurial diuretics may be toxic and for a condition in infants associated with severe malnutrition are not recommended; similarly, salt restriction or ionic exchange procedures would probably require accurate biochemical control which would be impracticable without the resources of a biochemical laboratory. In beriberi there are nearly always some signs of nerve involvement, but it may be pointed out that dietetic deficiencies are never single in practice, and protein deficiency is usually associated with vitamin deficiencies; for this reason alone, apart from the necessity of supplying lipotropic factors, adequate vitamin supplements should be given as well as plenty of protein.

Other causes of œdema will be associated with their appropriate clinical histories, physical signs, such as those of cardiac failure, or laboratory findings, for example, evidence of renal changes; but it must be remembered that malnutrition affects all the tissues, and some degree of dysfunction of almost any organ may be found. Accurate diagnosis will depend upon appropriate consideration of all the features of any individual case.

PROFESSOR F. MURGATROYD, M.D., F.R.C.P., D.T.M.

Contact Dermatitis from Watch-Strap

QUERY.—My father, aged sixty-three, has during the last three years bought three leather watch-straps and all of them have given rise to a localized skin eruption on his wrist. The eruption appears one or two days after the use of the new strap, and disappears two or three days after discontinuing its use. I assume the condition is allergic in nature, probably due to some 'dressing' in the strap. He suffers from no other allergic condition. Could you enlighten me on this small matter?

REPLY.—This patient is obviously sensitive to something in the leather of his watch-strap, it may be some dye or dressing ('dope' as it is known in the trade), but more probably it is chrome. Most leather is tanned with chrome nowadays, and this gave rise to considerable trouble in the Army, where extra quantities of chrome were put into the leather to prevent deterioration in tropical climates. The patient should be advised to wear a metal strap for his watch.

F. F. HELLIER, O.B.E., M.D., F.R.C.P.

Pre-Menstrual Dysmenorrhœa

QUERY.—I shall be grateful if you can help me in the diagnosis and treatment of the following case:—Female patient, aged forty. Two sons aged seventeen and thirteen, respectively. Dysmenorrhœa started about thirteen years ago after her second childbirth. Regular twenty-eight day cycle; flow normal. Pain in the back, which worries her most, starts two or three days before the periods, diminishing somewhat during the period. There is slight temperature during the periods, also pain on pressure over the lower right abdomen which she had never noticed before until in the course of examination some four months ago. This pain she has now observed persists slightly on pressure, between the periods. In view of the temperature and pain is treatment with penicillin or sulphonamides indicated?

REPLY.—The history of acquired dysmenorrhœa present for a few days before the periods and relieved by the flow would seem suggestive of either endometriosis or pelvic infection. The slight temperature at the periods would equally well be found if there is endometriosis. Before proceeding to treatment, an examination under anæsthesia should be done to determine if in fact either condition be present. If there is evidence of tubal swelling or thickening, then treatment by antibiotics and pelvic short-wave therapy would be indicated. If there is evidence of endometriosis or adenomyosis, then operation would be best at her age.

KENNETH BOWES, M.S., F.R.C.S., F.R.C.O.G.

ACTH and Cortisone in Chronic Bronchitis

QUERY.—Is there any evidence that either ACTH or cortisone would be useful in the treatment of long-standing chronic bronchitis?

REPLY.—There are no published observations on this question of which I am aware. Observations made in cases of pneumonia and peritonitis have shown that the clinical and tissue response to infective agents may be greatly reduced, but the organisms concerned may become widely disseminated. Mice, experimentally infected with pneumococci, have not benefited from ACTH (Kass *et al.*, 1951, *J. Lab. clin. Med.*, **37**, 180). It is well recognized that ACTH sometimes has dramatic effects on patients with status asthmaticus, the bronchospasm being relieved. A widely held current concept is that the adrenal hormones secreted in response to ACTH have an effect on blocking the normal antigen-antibody reaction in sensitized patients. Most observers are of the opinion that much more needs to be known about the response of the infected individual to these hormones before it can be safe, or advisable, to extend their use in clinical infections.

F. T. G. PRUNTY, M.D., F.R.C.P.

PRACTICAL NOTES

Antibiotic Treatment of Whooping-cough

A COMPARISON of the value of penicillin, aureomycin, chloramphenicol and terramycin in whooping-cough has been made by L. N. Haxen *et al.* (*Journal of Pediatrics*, July 1951, **39**, 1) in 150 children aged four weeks to eleven years. All the antibiotics were given by mouth—60 mg. per kg. body weight daily, in four doses—and treatment was continued for ten days. There was a history of previous immunization against pertussis in 47 of the patients over one year of age, and in three of the infants. The results are summarized in the following table:—

	Pen.	Aur.	Chlor.	Terra.
Patients under 1 year of age:	18	12	13	7
Duration of paroxysmal cough in hospital: average no. of days	21.8	15.6	13.8	14.1
Average no. of hospital days ..	22.8	15.9	17.2	18.4
Clinical estimate of benefit:				
Good	1	12	10	4
Equivocal ..	3	0	1	1
None	14	0	2	2
Patients over 1 year of age:	31	21	24	24
Duration of paroxysmal cough in hospital: average no. of days	18.0	17.4	13.5	14.5
Average no. of hospital days ..	19.2	18.7	16.3	16.8
Clinical estimate of benefit:				
Good	3	10	16	19
Equivocal ..	4	8	5	5
None	24	3	3	0

The average number of paroxysms of coughing per day decreased more rapidly among those receiving aureomycin, chloramphenicol and terramycin than in those receiving penicillin. There was a much more rapid disappearance of *H. pertussis* from the nasopharyngeal cultures in those treated with aureomycin, chloramphenicol and terramycin than in those receiving penicillin. There was some evidence that this early disappearance of *H. pertussis* may have delayed and reduced the antibody response. Toxic effects from the antibiotics were negligible, but treatment had to be stopped in two patients—one receiving aureomycin and one receiving terramycin—on account of their developing scarlet fever; in both, hæmolytic *Staph. aureus* were obtained in large numbers in pharyngeal cultures. In some cases there was a temporary exacerbation of cough during the days immediately following the cessation of treatment.

Postpartum Plasma in Rheumatoid Arthritis

THE results obtained from the use of postpartum plasma in eight patients with rheumatoid arthritis, who have been followed for two years, are reported by L. W. Granirer (*Journal of the American Medical Association*, July 14, 1951, **146**, 995). All the patients were bedridden or confined to a chair. Their ages varied from forty-eight to sixty-three years, and the duration of the arthritis ranged from six months to eighteen years. The postpartum plasma was given intravenously in doses of 250 ml. weekly. Improvement occurred in all eight patients, and usually began between the fourth and sixth injections. It consisted in 'relief of stiffness and decrease in pain, joint swelling, and inflammation'. 'Although there was not always a complete disappearance of symptoms, relief was greater than with any preceding therapy'. There was also an increase in appetite, weight and sense of well-being. The sedimentation rate remained raised in most cases. On cessation of treatment symptoms usually recurred within six weeks to a year, but there was a remission of eighteen months in one case. 'Resumption of postpartum plasma therapy was always effective when there was a recurrence of symptoms'. No side-effects were observed apart from one patient who developed urticaria which responded to antihistamines, and another who complained of sensitive breasts. As controls 'a similar group of patients' was given 250 ml. of plain plasma weekly, without any improvement in their condition. In an addendum it is stated that a further seven patients resistant to cortisone and ACTH 'have shown an excellent response to postpartum plasma'. This group consisted of five with rheumatoid arthritis, one with Still's disease, and one with exfoliative dermatitis and arthritis. It is considered that 'although complete relief was not achieved in all cases, the results obtained with postpartum plasma, on the whole, were as dramatic as any recorded for cortisone or pituitary adrenocorticotropic hormone (ACTH)'.

Progesterone in Rheumatoid Arthritis

THE effect of progesterone has been investigated in eight female patients with 'typical chronic active rheumatoid arthritis' of at least one-and-a-half years' duration, by P. J. Vignos, Jun., and R. I. Dorfman (*American Journal of Medical Sciences*, July 1951, **222**, 29). The progesterone was given parenterally in daily doses of 200 to

500 mg. for periods up to twenty-eight days. Only one patient received as much as 500 mg. daily, and for only three days. The results were disappointing: one patient showed 'marked' improvement, and two 'moderate' improvement. There were no serious side-effects. The expected suppression of menstruation occurred during treatment, and in one case persisted for three months. There was no change in the sedimentation rate, which was raised before treatment in all cases. The total urinary neutral 17-ketosteroid and corticoid excretions were studied in six cases. The only consistent change was in the patient who showed marked improvement: the 17-ketosteroid excretion rose from a pre-treatment level of 2.4 mg. per day to a maximum of 11.1 mg. per day while receiving 300 mg. of progesterone daily. The pregnanediol excretion was studied in five patients: with daily doses of 200 mg. of progesterone the urinary pregnanediol averaged 37 mg. per twenty-four hours, which is comparable to the excretion up to the fifth or sixth month of pregnancy. The percentage of progesterone excreted as pregnanediol varied between 9 and 40.5 per cent. The authors state that their series brings the total number of reported cases of rheumatoid arthritis treated with progesterone up to 56, and they summarize the results as follows: eight have shown 'marked' improvement, and 12 have shown 'moderate' improvement.

Liver Extract in Tuberculosis

THE value of liver as a dietary factor in tuberculosis has been investigated by J. Gershon-Cohen (*American Journal of Digestive Diseases*, July 1951, **18**, 215). The liver was prepared by cooking fresh chopped beef liver in a double boiler without water. It was allowed to simmer in its own juices for three to four hours by keeping the water in the lower part of the boiler at the minimum boiling level. By this method about 8 ounces (230 ml.) of broth are obtained from 1 lb. (540 g.) of liver. This broth, 'as a 4-ounce cocktail equivalent to a half pound of liver', was served daily to 31 tuberculous patients for three months. A control group consisted of 29 patients in the same group in the same sanatorium and in approximately similar stages of the disease. Apart from the liver, diet and medication were similar in the two groups. At the end of the three months the 'only clinically observed change was in the weight tables, and these showed that the individual average gain in weight of the liver group was 3.27 pounds as compared to 1.72 pounds in the control group'. In each group there were seven patients receiving streptomycin, and it was found that in the control group the patients receiving streptomycin showed an average individual weight loss of ½ pound, whilst in those receiving streptomycin in the liver group there was an average individual weight gain of 2½ pounds.

Treatment of Vertigo in Hypertension

As 'dramamine' (β-dimethylaminoethyl ether 8-chlorotheophyllinate) has been shown to depress labyrinthine function, I. R. Goldman *et al.* (*American Heart Journal*, August 1951, **42**, 302) investigated its effect in fifteen patients with 'vestibular disturbances complicating arteriosclerotic and hypertensive cardiovascular disease'. Thirteen of the patients, whose ages ranged from forty-one to seventy-five years, had hypertensive heart disease, whilst the other two, aged sixty-four and seventy-six, had arteriosclerotic heart disease. Most of them had tried other drugs previously with little or no effect. The dosage of 'dramamine' ranged from 25 to 100 mg. four times daily. No untoward side-effects were noted. Complete relief was obtained in ten cases, and marked improvement in three. No improvement occurred in two cases. In several of the cases it is reported that there was no recurrence of symptoms after the discontinuation of the 'dramamine'.

Facial Neuralgia as a Manifestation of Hypothyroidism

IN reporting 29 cases of facial neuralgia, F. B. Watts (*Annals of Internal Medicine*, July 1951, **35**, 186) draws attention to 'a common clinical syndrome which is often overlooked, namely, atypical pain about the face and neck frequently associated with the hypothyroid state'. His patients consisted of 25 women, aged twenty-three to fifty-nine (only one was over the age of fifty), and four men aged thirty-five, forty-three, fifty-eight and fifty-nine. The pain was not intense, but 'annoying and aggravating because of its chronicity'. It persisted for anything up to a week, and was described as 'a dull, transient pain behind the ear' or as a 'shooting pain centered around the ear, a dull annoying ache or throbbing in the neck over the carotid area, a drawing sensation or a pressure type of pain'. In some cases it occurred in the jaw. In twenty-one of the patients it was accompanied by chronic recurring headache, usually occipital or frontal. The pain, which was usually the presenting symptom, most commonly occurred when the patient was over-tired. Fatigue or 'easily tired' were common symptoms. Only one-third of the patients were overweight, and about one-half were unduly sensitive to cold weather. Relatively few complained of thinning

of the hair or dry skin. The basal metabolic rate was low in all cases, ranging from −7 to −28, with the majority lower than −15. Following the administration of thyroid, ¼ grain (16 mg.) thrice daily, or 1 grain (65 mg.) daily, there was marked improvement in 13, moderate in 11, and slight in four. One patient who could not tolerate even small doses of thyroid showed no improvement. The fact that improvement did not become evident until after a fortnight's treatment is taken to indicate that 'the improvement was a response to thyroid extract rather than a psychogenic response'.

Oral Procaine and Ascorbic Acid in Pruritus

SATISFACTORY results from the oral administration of procaine hydrochloride and ascorbic acid in the treatment of pruritus of allergic origin are reported by H. Luddecke (*Archives of Dermatology and Syphilology*, July 1951, **64**, 9). Details are given of ten cases treated in this way: atopic dermatitis (2), penicillin reactions (2), tetanus antitoxin reaction, dermatitis (2), food urticaria, contact dermatitis, urticaria. All responded satisfactorily and rapidly, except one case of atopic dermatitis in which there was an exacerbation of symptoms after the fourth dose of the procaine-ascorbic acid combination. In many of the cases there had been no response to antihistamines given before the procaine-ascorbic combination. The procaine and ascorbic acid were given in the form of tablets, each containing 250 mg. of procaine hydrochloride and 150 mg. of ascorbic acid. The usual dosage was one or two of these tablets four times daily. Reference is made to the low toxicity of procaine when given orally.

Complications of PAS Therapy

HYPOKALÆMIA is one of the recognized complications of treatment with *para*-aminosalicylic acid. As a result of a clinical investigation in tuberculous patients, A. H. Campbell and O. E. Neufeld (*Medical Journal of Australia*, May 19, 1951, **i**, 725) have shown that 'hypokalæmia which has developed following PAS therapy is due to an impurity in certain commercial preparations of PAS'. Patients were given 12 grammes of PAS daily, in the form of the potassium salt in aqueous solution for six days every week for twelve weeks. One group of patients was given a commercial preparation containing impurities, and the other was given a purer form of PAS which contained only 0.05 per cent. of impurity. Taking 16 mg. per cent. as the standard for serum potassium levels, it was found that of 37 patients receiving the 'impure' PAS, 16 had developed levels below this, compared with only 18 out of 158 patients who received the 'purer' PAS. In view of the fact that liquorice is often used as flavouring agent with PAS, the effect of liquorice on the serum potassium level was investigated, and it was found that with both 'impure' and 'purer' PAS there was a higher incidence of low potassium levels in those patients who were given the PAS flavoured with liquorice. It is therefore concluded that 'to prevent hypokalæmia as a complication only pure PAS should be administered. It is also inadvisable to use liquorice as a flavouring agent. . . . To prevent avoidable deaths it is necessary for the commercial preparation or PAS to be subject to rigid standards of control'. In a subsequent article, O. E. Neufeld (*Ibid.*, p. 727) gives details of relatively easy methods for testing for impurities in PAS. One of the most important of these impurities, and the one which is considered to be responsible for the hypokalæmia, is a dark-coloured ether-soluble compound. The exact chemical nature of this compound is not known, but it is probably a polymerized form of meta-aminophenol which is easily formed when *para*-aminosylicylic acid is exposed to heat or the influence of acids.

Treatment of Cardiac Arrest

THE value of intraventricular injection of 10 per cent. calcium chloride in the treatment of cardiac arrest is pointed out by J. H. Kay and A. Blalock (*Surgery, Gynecology and Obstetrics*, July 1951, **93**, 97) who give details of four cases treated in this way.

Case 1.—Ventricular fibrillation developed in a 5-year-old girl while being operated on for tetralogy of Fallot. The heart was defibrillated by means of the electrical defibrillator, but did not start beating. Three injections, each of 0.5 ml. of 1:1000 adrenaline hydrochloride, into the left ventricular cavity, at three-minute intervals, had no effect. Cardiac massage was continued, and after cardiac arrest had persisted for fifteen minutes 4 ml. of 10 per cent. calcium chloride were injected into the left ventricular cavity, and within five to ten seconds the heart began to beat vigorously. The child subsequently made a satisfactory recovery.

Case 2.—Cardiac arrest occurred in a 14-months-old baby while valvulotomy was being performed for pulmonary stenosis. There was no response to 0.5 ml. of 1:1000 adrenaline hydrochloride injected into the left ventricular cavity, combined with cardiac massage. A few minutes later, 3 ml. of 10 per cent. calcium chloride were injected into the left ventricular cavity, and in a few seconds the heart started beating. The duration of ventricular standstill was three minutes. The infant made a satisfactory recovery.

Case 3.—During valvulotomy for pulmonary stenosis in an 18-months-old infant the blood pressure became unreadable and cardiac action almost ceased. Following the injection into the left ventricular cavity of 3 ml. of 10 per cent. calcium chloride the heart's action improved immediately, and the operation was completed successfully.

Case 4.—Cardiac arrest occurred during an operation for tetralogy of Fallot in an 18-months-old infant. There was no response to cardiac massage or the injection of 0.5 ml. of 1:1000 adrenaline hydrochloride into the left ventricular cavity. As the heart beat remained ineffective, 0.5 mg. of atropine sulphate was injected into the left

ventricular cavity, without effect. When cardiac arrest had persisted for four minutes 2.5 ml. of 10 per cent. calcium chloride were injected into the left ventricular cavity, with immediate response. Shortly afterwards the heart became weak again; this time it responded to 0.5 ml. of 1:1000 adrenaline hydrochloride.

The authors conclude that their experience leads them 'to believe that calcium chloride may be life saving in the treatment of ventricular standstill arising spontaneously or following the successful electrical defibrillation of a heart in ventricular fibrillation. It is also extremely useful in preventing ventricular standstill in a heart with weak contractions'. They do not feel that calcium chloride is 'necessarily superior to epinephrine hydrochloride, but rather that the armamentarium of the surgeon in the treatment of these emergencies should include several cardiac stimulants. Irrespective of the cardiac stimulant used in the treatment of ventricular fibrillation, vigorous cardiac massage must be continued until an effective beat has been restored'.

Positioning for Cholecystography

An editorial in *Gastroenterology* (July 1951, **18**, 321) draws attention to work that has been done at the Mayo Clinic on the best position in which to place the patient for cholecystography so as to obtain a clear picture of the gall-bladder. As a result of this investigation it has been found that this position is an antero-posterior view with the patient lying on his right side. This permits the gall-bladder 'to gravitate somewhat away from the bowel', and therefore throws it clear of gas shadows. It also gives a better view of the bile ducts. It is said to have the further advantage that 'gallstones that cannot be identified in films taken in the ordinary position are plainly visible in a layer perhaps underlying the dye'. The editorial concludes: 'This technique is so satisfactory that it should perhaps be used routinely throughout the world. With it, the use of pitressin is rarely needed'.

Treatment of Bromide Intoxication

As a result of his findings in patients with bromide eruptions and in volunteers who took bromides, T. Cornbleet (*Journal of the American Medical Association*, July 21, 1951, **146**, 1116) recommends the use of ammonium chloride for the treatment of bromide intoxication. In the patients treated the administration of 6 g. of ammonium chloride (in enteric-coated tablets) daily caused a drop of just over 40 per cent. in the blood bromide level in four days, as compared with a drop of only 20 per cent. in those given the same amount of sodium chloride. The results in the volunteers were similar: a drop in four days of just over 40 per cent. in those receiving ammonium chloride, and a drop of just over 20 per cent. in those receiving sodium chloride. The effects of mersalyl and of urea were investigated in volunteers, but neither of these had any appreciable effect on the blood-bromide level. In the patients treated with ammonium chloride the increased excretion of bromide was accompanied by a correspondingly rapid healing of the bromide eruption. The position is summed up as follows: 'Diuretic chlorides have a dual action in removing bromides. They furnish chloride for displacing the bromide and at the same time are diuretics. We believe ammonium chloride is the most advantageous one to use. It is simple, cheap, and fairly safe. It should not be used when the kidneys are damaged. The enteric-coated tablets are not irritating to the stomach, and most people can take a total of 5 to 8 g. a day in divided doses without distress'.

Splenomegaly in Rheumatic Heart Disease

The incidence of splenomegaly in 80 consecutive patients with rheumatic heart disease admitted to hospital has been studied by W. L. Bennett and T. M. Durant (*American Heart Journal*, July 1951, **42**, 137). 'Definitely palpable enlargement of the spleen' was found in eighteen of these patients. In two cases it was due to subacute bacterial endocarditis, in two to portal cirrhosis associated with chronic alcoholism, and in one case to tuberculosis. In the remaining thirteen cases (16 per cent. of the total) 'no cause, other than congestive failure, was found to explain the splenic enlargement, and clinical evidence of congestive failure was minimal or absent in a few of these cases'. Tricuspid stenosis was present in one, and tricuspid incompetence in three. In three cases heart size radiologically was within normal limits. Ten of the patients had had symptoms of congestive heart failure for at least two years. Of the remaining three, one had no evidence of congestive failure, one had had symptoms of such failure only since the onset of pregnancy three months before, whilst the third had only had it for four months. In these three therefore it could not be attributed to long-standing severe portal congestion. On the basis of this study the recommendation is made that 'while it is admittedly very important to consider subacute bacterial endocarditis in all cases of rheumatic heart disease with fever and splenomegaly, the clinician must not place too much reliance upon splenomegaly as a finding favouring such a diagnosis'.

REVIEWS OF BOOKS

Modern Practice in Infectious Fevers (in two volumes). EDITED BY H. STANLEY BANKS, M.D., F.R.C.P., D.P.H. London: Butterworth & Co. (Publishers) Ltd., 1951. Pp. xxii and 989. Figures 319. Price 100s. per set.

CONTRIBUTIONS by fifty-two authorities from various countries are here combined to form a well-balanced symposium of modern teaching in infectious diseases. The first section is concerned with a general approach to the subject, consisting of chapters on ecology, epidemiology, laboratory aids to diagnosis and treatment, and immunization. After this, bacterial diseases are dealt with in the first volume, and virus, rickettsial, spirochætal, protozoal and mycotic diseases follow in volume two, in which the final section is on infectious fevers of unknown etiology. The principal fevers of the tropics are included, and the book encompasses a wider range of infections than is suggested by the word 'fevers'. It contains, for example, a chapter on giardiasis; this, with some other chapters, is inaccurately indexed in the tables of contents which precede each volume. The book is well produced, excellently illustrated, and entirely up to date, stress being laid on advances which have occurred during the last fifteen years. There is no doubt that when the wide scope of the book is realized it will become a valued work of reference among clinicians who deal with infectious diseases.

The Neuroses: Diagnosis and Management of Functional Disorders and Minor Psychoses. BY WALTER C. ALVAREZ, M.D. Philadelphia and London: W. B. Saunders Company, 1951. Pp. x and 667. Price 50s.

THIS is a fascinating book: it is an autobiography of a great physician and a great humanist. Although it purports to be a 'graduate course in the diagnosis and treatment of functional troubles', it is in fact almost a day book of experiment and observation by a consultant physician at work—'the best of what I have been able to glean in forty-five years of busy practice'. Written as it is by a physician, it shows the psychiatric problems that arise in the differential diagnosis of any symptoms, not fitted into any particular psychological theory, nor couched in psychiatric technical jargon. Almost every psychiatric question which the physician may meet, he can look up; and he will find a specific answer, not always satisfactory, but always sound and practical. A wealth of illustrative cases does not make a great textbook: there is little synthesis but great feeling and wonderful memory, supported by references to the best of psychiatric writings. There is also a fascinating bibliography of novels illustrating psychiatric problems, and many valuable medical references. The advice as to how to handle a 'nervous' patient, the need for making friends, the importance of being courteous, are valuable stabilizers in these days of hard scientific medicine.

Leaves from a Doctor's Life. BY SIR PHILIP PANTON. London: Wm. Heinemann Ltd., 1951. Pp. 232. Illustrated. Price 18s.

THIS is one of the most fascinating volumes of medical reminiscences that has been published for a long time. Sir Philip Panton was above all an individualist who was no respector of persons, certainly not the pompous and unctuous, and his comments on his contemporaries, seniors and juniors are never anything but frank: a frankness, however, which is never vindictive, but always tinged with that saving grace of humour which characterized him throughout life. His career—the son of a Dorset brewer, he was educated at Harrow, Trinity College, Cambridge, and St. Thomas's—during the greatest social revolution in the history of the professional classes (he was born in 1877) means that he has a wealth of social experience to draw upon. Take, for instance, his comment on Cambridge in his day: 'Then, we were faintly surprised to find that there were other schools than Eton, Harrow, Winchester, and Rugby. Even such a well-known school as Uppingham we had pretended to have been mainly peopled by boys expelled from Harrow and Eton'! The chapter on Harrow ends with an apologia of the Public School system which is all the more impressive for the almost brutal frankness with which the defects of the Harrow of those days have been lampooned earlier in the chapter. The same approach to life is apparent throughout the whole book—a complete lack of smugness or self-complacency, a critical evaluation of school, university and medical school, but an emphatic defence of their attributes and a devastating comparison with present-day standards. The book is permeated with one of the most wonderful fund of stories it has been the reviewer's lot to read for many a long day. Some of them possibly apocryphal, several of them well known, but all worth reading. His pen pictures of men such as Sharkey, Shattock, Hurry Fenwick and Henry Head, are brilliantly done. Perhaps the out-

standing chapter, however, is that entitled 'The Ministry of Health'. This exposure of the defects of the civil service, based upon his experience as advisor in pathology between 1939 and 1949 is all the more convincing in its trenchant criticism in that he has 'nothing but respect and admiration for the staff . . . the only incorruptible Civil Service in the world'. This is a book which will not only be read, but also bought and treasured by all who knew Panton, whether at the 'London' or in his Ministry days, and through them it will spread to a much wider public who will read and enjoy it for its picture of an England which is rapidly sinking into the mist of history.

The Catholic Doctor. By FATHER A. BONNAR, O.F.M., D.D., M.Sc. Fifth edition. London: Burns, Oates and Washbourne, 1951. Pp. 179. Price 12*s.* 6*d.*

Psychology, Religion and Healing. By LESLIE D. WEATHERHEAD, M.A., PH.D., D.D. London: Hodder and Stoughton, 1951. Pp. xx and 544. Price 25*s.*

THE new edition of 'The Catholic Doctor' by Father Bonnar brings up to date a book first published in 1937. It certainly achieves its object: 'The Catholic Church does not shrink from making her teaching definite'. And there is clear advice on medico-moral problems. We read that, if there is opposition between common medical teaching and the morality defined by the Church, the Church is right and must be obeyed. For the Catholic doctor and nurse the teachings on subjects such as abortion, sterilization and birth prevention are clearly expressed. Each chapter is self-contained. For all doctors they repay careful consideration; not least, perhaps, because of the question of cooperation in hospital services. The protagonists of euthanasia receive some well-directed blows. Sex teaching for the young should be individual and never to groups or classes: 'knowing something of human nature' he distrusts the biological approach. The psychologist should have definite standards. Father Bonnar pays tribute to the high mission of the doctor's calling. The medical knowledge in his book is sound and every doctor may profit from so wise a writer. He states that the priest's ministrations essentially have no medical purpose, but that outside his Church the clergyman is becoming more and more a medicine man.

Which statement applies to a remarkable book, 'Psychology, Religion and Healing', by Leslie D. Weatherhead, Minister of the City Temple. First, there is a review, down the ages, of the history of healing through the mind and spirit, with detailed explanations of how the miracles of the New Testament may have come about, which displays very extensive knowledge of the subject. Modern psychology is explained and discussed; and finally, the integrated personality which requires religious belief. It is a very stimulating book to read. It contains much knowledge and great experience of therapeutic psychology. The author's enthusiasm and deep conviction enhance his writing. He works in association with psychologists at his clinic, but he pleads for more cooperation from other members of the medical profession. Perhaps one might reflect on why this may not be easy to obtain. For example, in the chapter on 'intercession and prayer', we could believe with Dr. Weatherhead in its efficacy, but we could not accept some rather sensational case histories cited as proof. A controlled experiment is, of course, impossible. We should prefer faith to any attempt at proof. To our thinking, throughout the volume to illustrate his beliefs, there may be too many brief case records, which receiving publicity could lead to emotional states in other people. Some doctors must feel that members of the community are taking rather too much interest in their unconscious minds. Dr. Weatherhead wishes to have a Diploma in Psychology for ministers of religion. It would be a stimulating experience to work with him, but it might be a hazardous experiment to cooperate with a disciple. All general practitioners and hospital consultants are students of human nature. It is an older study than modern psychology, some of which will require modification to meet the needs of human fallibility.

Orthopædic Nursing. By MARY POWELL, S.R.N., M.C.S.P. Edinburgh: E. & S. Livingstone Ltd., 1951. Pp. xii and 400. Figures 210. Price 25*s.*

THIS book can be recommended to anyone interested in orthopædic surgery. It is written, says the author, primarily for nurses and physiotherapists. But it could with benefit be used by medical students, referred to by general practitioners, absorbed by postgraduates, and taken to heart by many orthopædic surgeons. For in it is the warp and woof of orthopædics—the essential threads which form the fabric of our art. The reputation of Hugh Owen Thomas, Robert Jones, and Agnes Hunt were not built on a long succession of failures or even of mediocre results. They were built on principles the application of which is here described minutely yet with attractive simplicity. Having been so entertained by the author it seems ungracious to criticize her work, but it must be

said that a place in the index might have been found for anterior poliomyelitis, that the precautions necessary for the safe use of a Thomas splint might be amplified, and that mention might have been made of the advantages of suitable splints over plaster of Paris in the treatment of Colles' fracture, although perhaps in view of the legends this last would be asking too much

Ambulation: Physical Rehabilitation for Crutch Walkers. By KENNETH A. DENING, B.S., FRANK S. DEYOE, JUN., B.S., and ALFRED B. ELLISON, B.S. New York: Funk and Wagnalls Company; London: Mayflower Publishing Co. Ltd., 1951. Pp. xxix and 188. Figures 109. Price 27*s.* 6*d.*

THIS book has a wider scope than its title suggests. It is a complete practical manual for paraplegics, telling them how to educate the unparalysed muscles of the trunk and upper limbs to perform new tasks, how to balance the trunk on the paralysed lower limbs, and how to become, so far as possible, independent of the help of others. It gives a practical system of exercises in the development of muscles and the performance of movements not required by the unparalysed, and step-by-step instruction in such necessary movements as getting from bed into a wheel chair and back into bed again, getting from a wheel chair into a bath, on to a toilet seat and into a motor car, and manipulating crutches for walking on the level and up or down slopes, for climbing stairs, for opening doors, turning corners, going backwards, and standing while one hand is in use. The authors speak from long experience, and they have provided a comprehensive series of photographs to illustrate the manœuvres they describe.

The Story of St. Luke's Hospital, 1750-1948. By BRIGADIER C. N. FRENCH, C.M.G., C.B.E. London: Wm. Heinemann (Medical Books) Ltd., 1951. Pp. viii and 212. Illustrated. Price 8*s.* 6*d.*

ST. LUKE'S HOSPITAL, which used to stand near the corner of City Road and Old Street, never had the reputation of the Royal Hospital of Bethlem. Yet, before it became the Woodside Hospital in 1930, and part of the Middlesex in 1948, it had a worthy history. It was founded like some of our teaching hospitals by City merchants drinking in coffee houses, yet not unmindful of the responsibilities towards the afflicted that their wealth gave to them. Its first physician, Battie, retired when he became President of the Royal College of Physicians. It was for 'poor' people, and the book contains much of interest to the psychiatric historian. Its reading stimulates the query, has not the time arrived when a trained historian should undertake the task of collating the history of the Bethlem, the Retreat, and indeed the psychiatric story generally as a coherent whole?

NEW EDITIONS

A Short Textbook of Midwifery, by G. F. Gibberd, M.B., M.S., F.R.C.S., F.R.C.O.G., in its fifth edition (J. A. Churchill Ltd., 25*s.*) is a credit to the author and his publishers and, for the price, few books can compete with it. Much of the text has been rewritten, but the author's task has been difficult as the book almost falls between the big and small categories, being, in places, too verbose. We agree with the criticisms already offered that the section on puerperal infections might be shortened, and furthermore, the text on uterine inertia and placenta prævia is much too lengthy. The tables of analysis of contracted pelvis and the causes of neonatal death and stillbirth are worthy of study, but it is a pity the author does not recommend morphine intravenously in shock, and that he omits to mention the use of pitocin by intravenous drip in the treatment of inertia. There are many points in which the author's text differs from teachings current elsewhere, but this is to be expected. The work, which contains 560 pages and 199 illustrations is well produced and can be confidently recommended to any student or postgraduate, for it is easily read and sound from beginning to end.

Textbook of Medicine, edited by Russell L. Cecil, M.D., SC.D., and Robert F. Loeb, M.D. (W. B. Saunders Co., 60*s.*). First published almost a quarter of a century ago, the high standing of this textbook is consolidated by the publication of the eighth edition. The contributors include many of the outstanding members of the profession in the United States, e.g. Fuller Albright, W. B. Castle, Philip Hench, Chester Keefer, George Thorn, and Paul White. Twenty new articles have been added in this edition. These include one on rickettsialpox by J. E. Smadel, and two by Tom D. Spies—on B_{12} deficiency and folic acid deficiency. In these days of expanding textbooks it is refreshing to learn that 'it is with considerable pride' that the editors 'report the shortening of the book by 136 pages'. Two features have always characterized this textbook. One is the emphasis upon physiological aspects of disease: for instance, the section on renal disease is introduced by a chapter on 'renal physiology

and tests of renal function', whilst that on cardiovascular disease is introduced by a chapter on 'pathologic physiology of generalized circulatory failure'. For future editions we would recommend the introduction of similar chapters in other sections, e.g., that on digestive disorders. The other characteristic feature is the relatively small amount of space devoted to treatment; this is never neglected but it is seldom discussed in detail. In view of the number of textbooks of therapeutics now available, this is a wise procedure, as it means that adequate discussion can be devoted to diagnosis and prognosis without rendering the book too unwieldy.

AMONG new subjects added to *Diseases in Infancy in Childhood*, by Wilfrid Sheldon, M.D., F.R.C.P., in its sixth edition (J. & A. Churchill Ltd., 40s.) are: the Fanconi syndrome, malignant malnutrition, periarteritis nodosa, meconium ileus, congenital hypoplastic anæmia, and recto-sigmoidectomy. Considerable revision has been undertaken and much new material added, including the use of folic acid in megalocytic anæmia, streptomycin and PAS in tuberculosis, and extended sections on pulmonary stenosis and patent ductus arteriosus, in the chapter on congenital heart disease, in which Blalock-Taussig's and Potts' procedures of anastomosis, and Brock's pulmonary valvulotomy are described in connexion with the former, and Gross's procedure of division of the ductus in the latter. The antibiotics, of course, occupy a prominent position among the new features, and in addition to their inclusion in the sections dealing with treatment, an appendix is added in which full particulars concerning the use of penicillin, streptomycin, chloramphenicol, and aureomycin are given. A useful table for conversion of the apothecary system of dosage to the metric is another welcome feature. The new edition is beautifully produced, and practitioners will find it a valuable addition to their working libraries.

The British Encyclopædia of Medical Practice, edited by Lord Horder, G.C.V.O., M.D., F.R.C.P. (Butterworth & Co. (Publishers), Ltd., 60s.). Volume six of the second edition ranges from gastritis to hypermetropia. Much of this volume is taken up by heart disease, which is dealt with by eleven authors in twelve chapters. The neurologists once again exhibit their gift for lucid exposition, e.g. Sir Charles Symonds' chapter on headache. An old-world note is struck by the appendix to the chapter on hydrotherapy, which gives a list of the 'better known' spas in this country and in Europe. The longest chapter is that on hernia by Harold C. Edwards. Revision has been reasonably extensive, but established teaching has not been discarded for the sake of novelty and newness. The teaching is on the whole sound, although one must deprecate the reference to paracentesis in the chapter on the pericardium. This is *not* a safe measure, and it is one which is seldom called for.

Clinical Heart Disease, by Samuel A. Levine, M.D., F.A.C.P. (W. B. Saunders Co., 40s.), in its fourth edition, has undergone thorough revision, particularly in the chapters on coronary thrombosis, bacterial endocarditis, and congenital heart disease. This is pre-eminently the practitioner's textbook of cardiology. Treatment is dealt with in more detail than is usual in such books, and the author does not hesitate to refer to lines of treatment which are still in the experimental clinical stage, but which are well worth considering in cases which are not responding to more conventional therapy. This is well exemplified in the discussion of the rôle of surgery in the treatment of heart failure. This is the type of information which is difficult to acquire except in the specialized journals, but which enables the practitioner to decide which of his cases may be worth sending to a teaching hospital where such facilities are available. Similarly, he will appreciate the allocation of all the data on electrocardiography to the final chapter, although British practitioners may consider 200 pages a generous allocation for this subject in a book of just over 500 pages. It is unnecessary to add that throughout the book the teaching is consistently sound—the author's name is sufficient guarantee of that.

IN view of the changes in the educational requirements for physiotherapists, and the institution of the Diploma for medical practitioners specializing in physical medicine, *Diathermy*, by William Beaumont, M.R.C.S., L.R.C.P., in its second edition (H. K. Lewis & Co., Ltd., 21s.) has been practically rewritten. The physical and physiological principles of long and short wave diathermy, epithermy and inductothermy, technique and apparatus, risks and dangers, the treatment of joints, soft tissues, suppurative conditions, the eye, ear, sinuses and skin, and systemic conditions are all covered, and there is a useful glossary of technical terms. The new edition is well produced and illustrated.

The contents of the November issue, which will contain a symposium on 'Diseases of the Ear', will be found on page xcii at the end of the advertisement section.

Notes and Preparations, see page 465.
Fifty Years Ago, see page 469.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'CIDAL' germicidal soap contains 2 per cent. hexachlorophene, a colourless, odourless and non-irritative substance which is stated to be '125 times more efficient than carbolic acid at 37° C. against *Staph. aureus*, and to possess the valuable property of being retained on the skin'. The use of 'cidal' soap is indicated in cases of acne, seborrhœa, impetigo, barber's rash, and those skin conditions in which soap and water are advocated, and also in the routine hygiene of the skin for the prevention of secondary infections, boils and athlete's foot. (J. Bibby & Sons Ltd., Liverpool.)

'ETHIDOL' sedative compound tablets, each containing ethinyl œstradiol, B.P., 0.01 mg., and phenobarbitone, B.P., 15 mg., have been prepared for use in the treatment of menopausal disturbances, the œstrogens exerting a beneficial action on the vasomotor and physical symptoms, and the phenobarbitone on the nervous symptoms, such as sleeplessness and irritability. The combination is also stated to have been found of value in cases of post-menopausal pruritus and senile vaginitis. Issued in containers of 25, 100 and 500 tablets. (British Schering Ltd., 229-231 Kensington High Street, London, W.8.)

'EUHÆMON' (vitamin B_{12}) is a sterile solution containing 50 micrograms of vitamin B_{12} (cyanocobalamin) per ml. It has been prepared for intramuscular injection in cases of pernicious and macrocytic anæmia, sprue, and subacute combined degeneration of the cord. The intramuscular injection of 'euhæmon' is stated to cause no discomfort, systemic or local reactions, and can be used in patients sensitive to liver extracts. Issued in ampoules of 1 ml., each containing 50 micrograms of vitamin B_{12}, in boxes of 6. (Allen & Hanburys Ltd., London, E.2.)

'MEPILIN' tablets of ethinyl œstradiol and methyltestosterone B.D.H. each contain ethinyl œstradiol, 0.01 mg., and methyltestosterone, 3 mg. Their use is indicated in the treatment of menopausal disorders, and it is claimed that the inclusion of methyltestosterone permits a marked reduction in œstrogen dosage, thus eliminating the withdrawal bleeding action of the œstrogens without being of sufficiently high dosage to promote hypertrichosis or other signs of virilism. Issued in bottles of 25 and 100. (British Drug Houses Ltd., Graham Street, London, N.1.)

'SENOKOT' is a pure vegetable laxative produced in the form of chocolate granules consisting of senna, cocoa, malt and flavouring, 100 g. of granules containing the active constituents of 15 g. Alexandrian senna pods, B.P. The preparation, which has a pleasant taste, may be eaten direct from the spoon or mixed with cold or warm milk. Issued in 2-ounce tins, and also in 2-lb. tins for dispensing. (Westminster Laboratories Ltd., Chalcot Road, London, N.W.1.)

'ADOPLAST' first-aid dressing is now supplied in a new dispenser pack containing 5-yard rolls, which are fed through a slot in the carton to permit cutting off of the required size. The dressing is then folded back and the lid closed, thus keeping the dressing clean and immediately available for use. Issued in cartons in three widths—1¼", 2", 2½" and 3". (Cuxson, Gerrard & Co. Ltd., Oldbury, Birmingham.)

NEW APPARATUS

THE ACOUSTICON-NEP CARDIOPHONE represents a cardiophone, incorporated with the ordinary stethoscope, which amplifies without distortion the heart sounds, and at the same time eliminates all other noises. The instrument, which weighs approximately 8¼ ounces, is small enough to fit into the breast pocket, and is supplied with three sizes of bakelite cones. The doctor's own stethoscope can be used by means of a bayonet adaptor, although a special stethoscope is available complete in a leather case. Also available is a suction chest piece for the use of anæsthetists or when it is desirable to have both hands free. A special feature is the four-position selectivity switch which permits 'acoustic focus' on the heart sounds by elimination of respiratory noises. (General Acoustics Ltd., 122 Wigmore Street, London, W.1.)

MEDICAL FILMS

'*Some Aspects of Muscle Relaxants*' (16 mm. colour sound film—running time 28 minutes) has been made by Messrs. May & Baker Ltd. in collaboration with the Department of Anæsthetics, St. Thomas's Hospital. It is divided into three main sections: 'pharmacology', 'clinical uses in anæsthesia', and 'clinical uses in electro-convulsion therapy'. In the first part the mode of action of muscle relaxants is demonstrated chiefly by diagrams; in the second, the clinical uses of 'flaxedil' brand gallamine triethiodide in anæsthesia are shown; in the third a demonstration of the use of 'flaxedil' in electro-convulsion therapy is given. Arrangements for the film to be shown to medical, pharmaceutical and nursing groups can

CONTINUED ON PAGE 466

be made on application to May & Baker Ltd., Dagenham, Essex, or to their branches overseas.

'*Nitrous Oxide-Oxygen Anæsthesia in the Dental Surgery*' (sound film—running time 47 minutes) has been produced by the British Oxygen Co. Ltd. for showing at the Congress of Anæsthetists. The film opens with pictures demonstrating general surgical and dental anæsthesia, and then proceeds to modern dental anæsthesia and its development from the early stages. Next, a sequence of pictures taken at the Eastman Dental Hospital are shown illustrating actual cases and the administration of nitrous oxide-oxygen, ethyl chloride and vinyl ether. The effects of premedication with intravenous thiopentone are also shown. The final section is devoted to modern anæsthetic apparatus, including the Walton portable apparatus designed for the use of practitioners. The film is available for exhibition to medical or dental audiences on application to The British Oxygen Company Ltd., Grosvenor House, Park Lane, W.1.

A NEW MEDICAL BOOKSHOP

A NEW bookshop, 'Lloyd-Luke (Medical Books) Ltd.', has been opened opposite the Middlesex Hospital, at 22 Cleveland Street, London, W.1. The proprietors are Mr. W. Richard Lloyd and Mr. Douglas Luke, both of whom have been connected with medical publishing firms for many years. Textbooks, stationery, journal subscriptions, and medical publishing comprise the activities of this new firm, and we wish it success in its venture.

PUBLICATIONS

An Integrated Practice of Medicine. Vol. V. By H. T. Hyman, M.D. The first four volumes of this compendious textbook of medicine were reviewed some four years ago (*The Practitioner*, 1947, **159**, 80). Volume V is described as a 'progress volume' published as a supplement to 'summarize recent and pending contributions to the medical sciences'. It also contains a series of indices to the five volumes. All those who possess the first four volumes will certainly wish to have this 'progress volume', and it will also be of use by itself. It is commendably up to date, containing sections, for instance, on cortisone, ACTH, chloramphenicol, aureomycin, terramycin, the thiosemicarbazones, and hyaluronidase. By contrast, the section on the sulphones is curiously out of date. On the whole the reviews of the present status of therapeutics are sound and balanced, as in the section on hypertension (pp. 4360-1), but both selectivity and accuracy are occasionally sacrificed in the attempt to be comprehensive, as in the section on pulmonary tuberculosis (para. 29, p. 4613). (W. B. Saunders Co., price 50s.)

Black's Medical Dictionary, by J. D. Comrie, M.D., F.R.C.P.ED., and William A. R. Thomson, M.D., in its twentieth edition (A. & C. Black, 30s.) has been entirely reset, a number of the illustrations (which total 400) have been replaced by new ones, and ten full page plates, some in colour, added. This dictionary is unique in that in addition to descriptions of the symptoms, sections on treatment are added, and in the case of practical procedures, for example 'syringing the ear', there is an accompanying illustration. Among the many new additions is a section on B.C.G. immunization against tuberculosis. A particularly useful section appears under the word 'dosage' in which most of the drugs in general use with their dosage in imperial and metric measures are given. The new setting, with the subjects in heavy capitals, is a great improvement.

Deutsch-Englisches, Englisch-Deutsches Wörterbuch für Ärtze, by Fritz Lejeune. Volume 1 (German-English) of this new medical dictionary has just been published. The work had its origin in an American prisoner of war camp during the 1939-45 war, and thus some Americanisms have naturally been included. It is a practical and up-to-date work and current chemical and laboratory terms are given. In his preface the author states that the work has been compiled chiefly for the use of young colleagues who, owing to the changed post-war conditions, are now brought into contact with English-speaking peoples, and he has included descriptive phrases and marks of pronunciation for their guidance. The typography is excellent. (Stuttgart: Georg Thieme Verlag, DM 24.)

'*Wonderfully Made*'. By A. Rendle Short, M.D., F.R.C.S. This is a simple up-to-date account of human physiology which avoids technical terms and gives simple analogies. Embryology is skilfully summarized in 12 pages, and a special feature is a discussion of the problem of man's origin, to which the last chapter is devoted. Those, such as student nurses, with some previous knowledge of physiology, and medical students bewildered by the detail of the subject, will benefit most from this book, but lay persons, too, will find it of great interest. (Paternoster Press, price 6s.)

Social Service Problems, published by the Conservative and Unionist Central Office, well merits its subtitle 'Everyman's Guide'. In its 40 pages doctors, social workers, administrators, and patients will find succinct and reliable infor-

CONTINUED ON PAGE 468

THE CHEMOTHERAPY OF TUBERCULOSIS WITH P.A.S.

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G.M. 77

mation, with the necessary addresses, on such questions as industrial injuries insurance, National Health Service, housing, war damage, post-war credits, aliens, emigration, wireless sets for the bedridden, and voluntary organizations for old peoples' welfare. (Abbey House, Victoria Street, London, S.W.1, price 1s. 3d.)

Fussgymnastik mit Kindern, by Martha Scharll. In this little booklet the author, who is teacher of corrective exercises at the University Orthopædic Clinic in Munich, describes the different exercises practised for the correction of abnormalities and the normal development of the feet in children. The illustrations are accompanied by short descriptive captions which can be easily understood even by those who have no great knowledge of the German language. From the children's faces illustrated it would seem that the whole procedure appeals to them as an exciting game, while at the same time achieving the desired object. It is a delightful production, and will be welcomed by pædiatricians and physiotherapists. (Stuttgart: Georg Thieme Verlag, price DM 2.90.)

FORTHCOMING PUBLICATIONS

MESSRS. EYRE & SPOTTISWOODE'S autumn list includes new and completely revised editions of the following medical books: *Practical Procedures*, a 'Practitioner' Handbook; '*The Practice of Endocrinology*', by Raymond Greene; *Treatment by Manipulation*', by H. Jackson Burrows and W. D. Coltart; also '*Patterns of Sexual Behaviour*', by Chellan S. Ford and Frank A. Beach. New impressions are now in hand of '*Diseases of the Heart and Circulation*', by Dr. Paul Wood, and of '*The Early Recognition of Disease*' ('Practitioner' Handbook). Full list on application to 15 Bedford Street, London, W.C.2.

MESSRS CASSELL & COMPANY LTD. announce the forthcoming publication of: 'Relief of Pain in Childbirth', by W. C. W. Nixon and Shila Ramsom; 'Patterns of Marriage', by Eliot Slater, and 'Tumours of the Eye', by Algernon B. Reese (37/38 St. Andrew's Hill, London, E.C.4.)

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the year ended 31st March, 1950. Part II, 'On the State of the Public Health', is the first annual report presented by Sir John Charles as Chief Medical Officer. Taking stock of the nation's health in 1949, he includes on the credit side the lowest death rates on record for children in the first, second, third, and fifth years of life, and new low records for babies in the first year and in the first month of life, and for stillbirths. Deaths from tuberculosis showed a 'remarkable decline' of 10 per cent. On the debit side he includes cancer deaths and increase in food poisoning and poliomyelitis. Heart, vascular, and respiratory diseases, influenza, and old age accounted for 61.2 per cent. of all deaths in the year—4 per cent. more than in 1948. Only four cases of indigenous malaria were reported. More than 1,200,000 persons were examined by mass miniature radiography, bringing the total since 1943 to over 4,000,000; 95 per cent. had no abnormal chest condition. The report emphasizes the necessity for reducing home accidents as an important part of modern preventive medicine, the number of fatal domestic accidents fluctuating between five and six thousand every year, of which 20 per cent. are among children under five, and 60 per cent. among people over sixty-five. (H.M. Stationery Office, price 6s.)

The Application of Scientific Methods to Industrial and Service Medicine is the title of the proceedings of an important conference held on behalf of the Medical Research Council in London from March 29 to 31, 1950, under the Chairmanship of its Secretary, Dr. H. P. Himsworth. The papers presented included 'General principles of field surveys' by A. Bradford Hill; 'A survey of sickness incidence' by D. D. Reid; 'Occupational factors in peptic ulcer' by R. Doll; 'Occupational and domiciliary factors in pulmonary tuberculosis' by Alice Stewart; 'Fluorosis and berylliosis as industrial and community health hazards' by Donald Hunter; a symposium on 'The improvement of human performance by laboratory studies'; 'Some problems in the investigation of coalworkers' pneumoconiosis' by C. M. Fletcher; and 'Problems in the physiological assessment of shortness of breath' by J. C. Gilson. (H.M. Stationery Office, price 3s.)

Annual Report of the Board of Control to the Lord Chancellor for the year 1950 discusses the increasing problems of the care and nursing of old people with mental illness, due mainly to the greater proportion of 'over-65's' in the community. Regional Hospital Boards have been urged to make suitable provisions for them outside mental hospitals. The total number of patients under treatment for mental illness at the end of 1950 was 147,546 (63,208 men and 84,338 women), the rising proportion of voluntary patients admitted to hospital being emphasized. Shortage of accommodation and of nurses again proved to be a major difficulty. The number of cases of tuberculosis arising in mental hospitals continues to fall (H.M. Stationery Office, price 6d.)

THE PRACTITIONER: 50 Years Ago. See page 469

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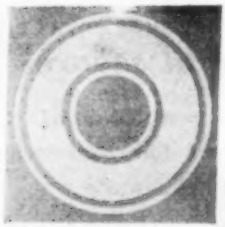

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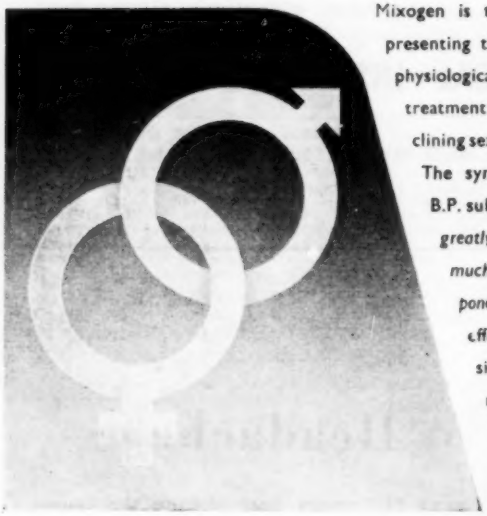

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THE PRACTITIONER

Fifty Years Ago

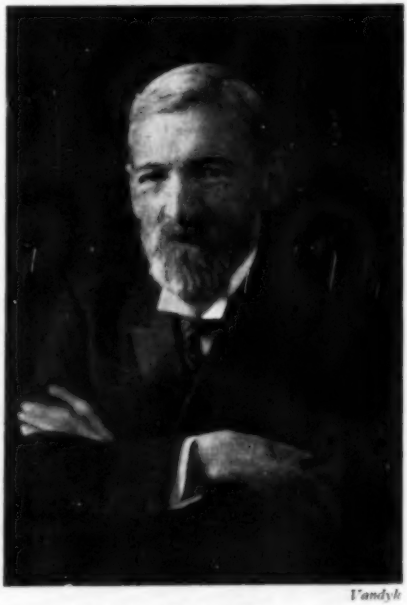
'We only learn at intervals, we forget all day long'.—Schopenhauer.

OCTOBER, 1901

THE introductory address continues to be as unpopular today as it was fifty years ago when the Editor wrote: 'It is evident that the Introductory Address is doomed, and if it still lingers superfluous on the stage at a few schools it is slowly but surely dying a natural death. Compare the half-dozen hardy perennials of this year with the tropical luxuriance of oratory which marked the opening of the schools even ten or fifteen years ago. As one may gauge the importance of a statesman from the amount of space given by the newspapers to his public utterances, so one may measure the decay of the Introductory Address by the place which it now occupies in journals which have a large stock of "copy" to draw upon. The time was . . . when the whole space usually devoted to "originals" in the *British Medical Journal* was given up to Addresses; this year a few abstracts of these discourses are tucked away after the more important papers'. Describing the addresses as 'lay sermons', 'The Month' continues: 'The whole thing is a solemn farce, for the preacher himself does not believe the smooth things which he prophesies, while his hearers are according to their various natures amused or disgusted by the contrast between the noble sentiments expressed and the sordid realities of professional life as they know them'.

Under the heading 'Echoes of the Tuberculosis Congress', reference is made to a criticism expressed by the *Gazette Hebdomadaire des Sciences Médicales* of Bordeaux that the organization of the band of French visitors was 'lamentably defective, with the result that they were mere isolated atoms lost in the whirling crowd of varied nationalities'. The German contingent, by way of contrast, was 'drilled to a military precision of movement and united action . . . each German leader goes to these gatherings of the medical clans, like a Highland chieftain of the olden time, "with his tail on", that is to say, with a full body-guard of dhuinewassails. Whenever the great man opens his mouth his henchmen make the welkin ring with their applause . . . They go to entertainments in solid phalanxes, take buffets by storm, and hold them against all comers. It is a triumph of discipline. But the growing predominance of the German factor at Congresses is becoming a nuisance, and also a danger, for it tends to drive out less aggressive nationalities, and there is a fear of the Congresses thus ceasing to be international. The Germans have many great qualities, but it cannot be denied that in DeQuincey's phrase, courtesy flows from your ordinary Teuton as naturally as milk from a male tiger. This circumstance does not make him popular in a mixed society'.

The symposium on orthopædics is continued from the previous number with a long article on 'Fractures of the Lower Extremity' by H. L. Barnard, M.S., F.R.C.S., Assistant Surgeon to the London Hospital, whose improved method of treating the separated lower epiphysis of the femur (1899) attracted considerable attention at the time. At the London Hospital where Sir Frederick Treves had advocated delay in operating in acute appendicitis, Barnard urged



Vandyk

Sir James Berry (1860—1946)

FIFTY YEARS AGO—*continued*

immediate operation. In the history of surgery he will long be remembered for his paper on 'Surgical Aspects of Subphrenic Abscess' (1908). F. C. Wallis, Assistant Surgeon, Charing Cross Hospital, writes on 'Treatment of Paralysis and Muscular Atrophy after the Prolonged Use of Splints or of an Esmarch Cord'. Wallis, who was knighted in 1911, was widely known outside the medical profession as the founder of the Union Jack Club for Soldiers and Sailors. Lydia Leney, M.D. Brux., discussing 'Gastric Flatulence and its Relation to the Gastric Secretion', rather daintily prefers the term 'excessive volatile acidity of the stomach' to 'flatulence'.

'A Review of the Medical Sciences' begins with a survey of 'Plastic Operations upon the Urethra and Bladder' by B. A. Moynihan, M.S., F.R.C.S., then Assistant Surgeon, Leeds General Infirmary. Sir James Berry's 'Diseases of the Thyroid Body and their Surgical Treatment' receives a long and laudatory review: 'Mr. Berry has supplied English readers with a work on this subject which is worthy of British surgery and redounds greatly to the credit of the writer. From merely a literary standpoint the book is well written, for without being unduly concise the material is not spun out, so that reading it is a pleasure. It is well mounted, and deserves a large measure of favour and success'. When in 1886 the Royal College of Surgeons of England announced the subject for its Jacksonian Prize Essay to be 'The Pathology, Diagnosis, and Surgical Treatment of Diseases of the Thyroid Gland', Berry who had recently become a Fellow of the College, spent six weeks in Switzerland, talking to surgeons, general practitioners, and patients, and studying specimens in museums. Though his essay was successful, the author modestly postponed its publication for fifteen years. The final note of pessimism sounded in the book, 'Reviewing the whole subject of the operative treatment of exophthalmic goitre, it seems to me that it may reasonably be doubted whether surgical treatment is not on the whole worse than useless', has not been vindicated by the passage of time, and it is interesting to find this passage deleted in the author's interleaved copy, which was intended to form a second edition and which is now preserved in the Library of the Royal Society of Medicine. Sir James Berry is immortalized in the annals of surgery as the pioneer of thyroid surgery in the English-speaking world.

The treatment of diabetic coma is now so clearly defined and so scientific that the following extract from 'Practical Notes' reads like a tale from almost mediæval times:—'In diabetic coma, Dr. Herzog, of Berlin, uses from 3 to 5 per cent. of bicarbonate of soda or chloride of sodium. Dr. Lépine, of Lyons, uses:—Sodium chloride ℥ i, Sodium bicarbonate ℥ iii, Water 1 quart'.

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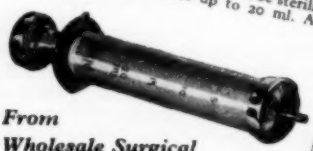

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